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Organicism and Reductionism in Cancer Research: Towards a Systemic Approach

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In recent cancer research, strong and apparently conflicting epistemological stances have been advocated by different research teams in a mist of an ever-growing body of knowledge ignited by ever-more perplexing and non-conclusive experimental facts: in the past few years, an 'organicist' approach investigating cancer development at the tissue level has challenged the established and so-called 'reductionist' approach focusing on disentangling the genetic and molecular circuitry of carcinogenesis. This article reviews the ways in which 'organicism' and 'reductionism' are used and opposed in this context, with an aim at clarifying the debate. Methodological, epistemological and ontological implications of both approaches are discussed. We argue that the 'organicist/reductionist' opposition in the present case of carcinogenesis is more a matter of diverging heuristics than a claim about theoretical or ontological (ir)reducibility. As a matter of fact, except for the downward causation claim, which we question, we argue that the organicist arguments are compatible with the reductionist approach. Moreover, we speculate that both approaches, which currently focus on specific entities i.e. genes versus tissues, will need to shift their conceptual frameworks to studying complex arrays of relationships potentially ranging over several levels of entities, as is the case with 'systems biology'.

1. Introduction

Despite several decades of heavily funded research, cancer still kills millions of people every year.[1] As a matter of fact, scientific research on this disease is a major societal issue; it has also become the theater of a stimulating debate on epistemological stances, becoming a renewed battlefield for organicism and reductionism. These two approaches have led to the formulation of two opposing theories of cancer: on the reductionist side, the Somatic Mutation Theory (SMT) explains cancer by appealing to genetic mutations, while on the organicist side, the Tissue Organization Field Theory (TOFT) locates the cause of cancer in a disruption of tissue organization. Recently, Marcum (2005) analyzed how organicism and reductionism, taken as metaphysical presuppositions, shaped carcinogenesis research and in turn were shaped by it. In the present contribution, we aim

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[1] The International Agency for Research on Cancer, which is part of the UN World Health Organization, estimates the global mortality rate due to cancer at some 8 million deaths per year (based on 2002 data: see online epidemiology data on http://www-dep.iarc.fr/); more recent estimates point to 10 million deaths per year worldwide (Khayat 2005).

more specifically at clarifying the debate on these two opposing epistemological stances with a view to understanding more specifically on which grounds they really diverge, or not, in cancer research. We start by briefly recalling the two views, relying on Robert Weinberg and coworkers' research as representative of the SMT, and on the works of Ana Soto, Carlos Sonnenschein and coworkers as illustrative of the TOFT.[2] Following Ayala (1974), we then articulate our analysis of organicism/reductionism along three dimensions: methodological, epistemological and ontological. For each of these dimensions, we question the extent to which the SMT and the TOFT stances diverge. Finally, we focus on reasons for both approaches to ultimately converge and articulate one another into a 'systems biology' approach to carcinogenesis. Yet in turn we raise the question whether the usage of complex systems theories in carcinogenesis might or not open the back door to new kinds of emergence and irreducibility.

2. Two opposing theories of cancer

The advances in molecular biology over the last three decades have paved the way for a genetically anchored theory of cancer, the Somatic Mutation Theory (SMT). This theory probably qualifies as 'mainstream theory' in that it has harvested most funding on cancer research so far. It posits that cancer has its causes rooted in genetic malfunctioning at the cellular level. This view of cancer can be traced back to the work of Boveri (1914) and is today typically illustrated by the research of Weinberg and coworkers. This reductionist approach was made explicit in Weinberg's book, *One Renegade cell* (1998) and emphasizes the key role of a single mutated cell in carcinogenesis. An alternative view comes from the tradition of developmental biology, placing the organism at the focal point of research, and finds its origin in the work of Waddington (1935) and Needham (1936). According to this view, the causes of cancer are to be searched not at the genetic level but at the tissue level: for the proponents of the Tissue Organization Field Theory (TOFT), cancer originates from a disruption of tissue organization. This hypothesis has been investigated for instance by Bissell and coworkers (1984); it is also typically how Soto and Sonnenschein define their conceptual framework for research on carcinogenesis, an organicist point of view that they have developed in their joint book *The Society of Cells* (1999), while making their epistemological posture even more explicit (Soto and Sonnenschein 2005; for a shorter treatment, see Soto and Sonnenschein 2004).

The approach of the Somatic Mutation Theory, according to which the cause for cancer is to be searched for at the genetic level, has often been qualified as an example of 'reductionism', and more precisely of 'genetic reductionism'. The anchoring of the SMT within the genetic reductionist paradigm has really emerged in the 1970's: at that time, it was established that a considerable number of carcinogenic chemicals could cause

[2] Cancer research is an extremely complex field of scientific investigation. In this paper, we focus on two ways of looking at cancer development as illustrated by two specific research teams. This bipolarization should not be seen as an oversimplification of the cancer research field nor of its history: it serves as an anchor point only for our philosophical discussion on organicism and reductionism. For historical views on cancer research, see for instance van Helvoort (1999) or Morange (1997).

genetic mutations. Later, it was also found that some so-called tumor viruses – also named transforming genes or oncogenes – could lead to the development of tumors by carrying mutated genes into the infected cells. A next discovery established that these external oncogenes were similar to genes already present in the cell itself; at that point the search for a genetic cause of cancer shifted from exogenous to endogenous, and several endogenous oncogenes were identified as mutated forms of normal cellular genes. The full complexity of cancer was yet to come as it was later found that some cases of carcinogenesis could only be explained as a multi-step process involving several oncogenes, as well as potentially one or several anti-oncogenes or tumor suppressor genes (for further details, see Weinberg 1998; Hanahan and Weinberg 2000; Han and Weinberg 2002). To date, more than 100 oncogenes and 15 anti-oncogenes have been identified. The cell cycle clock was also found to be of importance, as well as genes responsible for cell immortality. The full-blown picture of today's understanding of the causes of cancer as depicted by Weinberg has extended well beyond intra-cellular genetic causes and now also involves many molecular pathways including communication signals between cells: carcinogenesis is now seen as resulting from the acquisition by tumor cells of six distinct capabilities, namely "self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis" (Hanahan and Weinberg 2000, 57). Each of these capabilities can be acquired by different pathways at the molecular level; for instance, self-sufficiency in growth signals – resulting in autonomous cell growth and proliferation – can be acquired through alteration of either extracellular growth signals, transcellular transducers of those signals, or intracellular circuits that translate these signals into action. These six acquired capabilities would even be enabled by a seventh characteristic, genome instability, sometimes also called 'increased mutability'. The formulation of the SMT has therefore been more recently recast in terms of "heterotypic interactions between incipient tumor cells and their normal neighbors" (Hanahan and Weinberg 2000, 67). The early and extreme 'genetic reductionism' according to which cancer is caused by a faulty gene in a single renegade cell has been adapted to accommodate the complexity of carcinogenesis and the multitude of molecular pathways leading to proliferation of tumor cells. Yet it remains that the SMT focus on molecular entities as the major loci for explanations of carcinogenesis.

On the other hand, the approach to cancer proposed by Soto and Sonnenschein and their team is anchored in tissue research. The Tissue Organization Field Theory (TOFT) finds an explanation of cancer in terms of disruption of tissue organization as opposed to expression of a faulty gene. Let us recall that tissues of an organ are typically composed of two groups of cells: the parenchyma, made out of the functional cells of that specific organ, and the stroma which keeps the parenchyma in place and is the name for the structural cells of the organ. The TOFT is based on two main premises: (i) proliferation is the default state of all cells, and (ii) carcinogens initially act by disrupting the normal interactions that take place among the cells in the stroma and parenchyma of an organ (Soto & Sonnenschein 2005). According to this view, in healthy organs, the cells of the stroma and of the parenchyma act reciprocally upon each other by means of interactions

that started earlier, at the time of organogenesis and cell differentiation. Among other things, these interactions determine the shape and the structure of the organ, the differentiation of its diverse cell types and exert a negative control on cell proliferation, i.e. they induce the cells not to proliferate, contrary to what they would do under their default state. The disruption of these normal interactions between stroma and parenchyma results in abnormal tissue structure, removal of the negative control mentioned above, and therefore in cell proliferation. Hence the cause of carcinogenesis is located in the disruption of tissue organization.

For the proponents of the TOFT, the SMT program operates a 'reduction' by which it searches for causes of carcinogenesis at the level of the genes and molecular components of cells, and not at the aggregate level of tissues: cancer is viewed as an intra-cellular problem, caused by mutations in the DNA of the cancer cell itself. According to the TOFT view, the critical level at which carcinogenesis causes should be searched for is the tissue level because it typically is the level at which, using biopsy, a definitive diagnosis of cancer can be made (Soto and Sonnenschein, 2005, 112). Soto and Sonnenschein define genetic reductionism as follows: "a great number of biologists insist that explanations should always be sought for at the gene and/or gene product level, regardless of the level of organization at which the phenomenon is observed. This stance, genetic reductionism, […] predicates that everything in biology may be reduced to genes because the genome is the only repository of transmissible information" (2005, 104). For the TOFT proponents therefore, the approach followed by the SMT researchers is too restrictive and leads to a narrow framing of the issue purely in terms of genes and molecular expressions; it even dooms the cancer research program itself at its very roots, and is the main reason for "why it should be dropped and replaced" (Sonnenschein and Soto, 2000); in other words, the SMT approach is criticized for oversimplifying the causal determination of cancer to genes and molecules within cells, thereby ruling out the investigation of other potential causes such as tissue organization.

As substitute to genetic reductionism, advocates of the TOFT propose to adopt organicism: cancer is seen as a problem akin to histogenesis or organogenesis gone awry, and thus to a problem of developmental biology. In the words of Soto and Sonnenschein, organicists "choose to work at the level of organization at which the studied phenomenon is observed and venture gingerly into lower levels of organization, moving gradually through the diverse hierarchical levels of complexity, rather than jumping from phenotype to gene. Moreover, since they acknowledge emergent phenomena, their incursions into lower levels must be followed by a synthesis of how lower level phenomena bear upon upper level phenomena" (Soto and Sonnenschein 2005, 104). It is such claims that we wish to analyze more precisely.

3. A methodological divide: heuristic principles

The questions of organicism/reductionism pertaining to a methodological domain typically encompass issues concerning the diversity/unity of scientific method as well as of research strategy. According to methodological reductionism, all domains of science

should use a unique method – rather than several ones – to justify their theories. This method includes, on the one hand, usage of the experimental method – confronting hypotheses to experiments – and, on the other, reliance on observations as a fuel to the discovery process. Proponents of the SMT or of the TOFT do not precisely mention these very generic principles of methodological reductionism and on which we would expect them to agree. The debate indeed appears to concern not so much the scientific method *per se* but more specifically orientation of the research strategy: a major divide between the two approaches to carcinogenesis does concern heuristics. Indeed, the SMT and the TOFT appear in disagreement when it comes to the working hypotheses they use as guidelines to their investigation and discovery processes. The proponents of the TOFT claim to follow an organicist or holist approach, whereas the SMT is labeled reductionist in this context. For the TOFT proponents, the process of discovery is guided by the search for explanations formulated at the level of tissues, which is the level of observation of cancer by biopsy (Soto and Sonnenschein 2005, 112). On the opposite for the SMT proponents, the process of discovery involves the search for explanations formulated in terms of cellular or genetic/molecular entities, therefore respectively one and two levels of explanation below the tissue level. It is therefore on this heuristic dimension that the two approaches part. The underlying issue is of course how to operate the first 'cuts' when one is investigating a very complex problem, how to select the features which will prove relevant and decisive in providing a satisfactory explanation. In this respect, the development of a theory is a historical process strongly influenced by its underlying heuristic assumptions. For the SMT, since cancer is assumed to be a disease caused by mutated genes, the investigation of carcinogenesis focuses on the search for faulty genes. For the TOFT, cancer development is assumed to be a matter of disrupted tissue organization; hence the search for cancer causes in tissue disruption patterns.

Looking specifically at these heuristic principles, Marcum (2005) has recently highlighted the extent to which they might influence the scientific practices used to examine the nature of cancer in design of experiments and interpretation of experimental results. Marcum calls these heuristic principles "metaphysical presuppositions" and points to the fact that the "metaphysical presuppositions scientists are committed to in their practices are indeed 'heterogeneous' elements, which not only shape those practices and the generation of scientific knowledge […] but, in turn, are also shaped by those practices and knowledge" (2005, 32). Such heuristic principles should not be seen as static elements but, more accurately, as dynamic and malleable components of research work, depending on the progress of scientific investigations. Accordingly, the heuristic divide between the SMT and the TOFT proponents might very well be a historically-contingent situation only.

Let us note that questions on the historical consequences of such a heuristic-contingent development of cancer theories are not absent from arguments exchanged by both sides. Soto and Sonnenschein for instance clearly refer to the TOFT as a better – in the sense of 'faster' – scientific route towards a full understanding of – and therefore a cure of – cancer compared to the SMT; of course, proponents of the SMT argue opposite-wise, and, obviously, only time will tell in due course which of these two approaches to carcinogenesis was right, if any. Yet for Soto and Sonnenschein, time-delay is one of the

critical consequences of having adopted wrong heuristic principles: "a comprehensive understanding of carcinogenesis in general […] has been delayed because of epistemological issues" (Maffini *et al*, 2004, 1495). And this fact might have an impact on the life of millions of people. By pointing to a heuristic-contingent development of theories, the study of organicism/reductionism in cancer research raises central questions in the 'science and public policy' arena, namely questions about the evaluation of heuristic principles and research strategies beforehand, and the induced societal responsibility of associated choices.

The heuristic-contingent development of cancer theories also raises a question of epistemic dimension. Indeed, if one observes that different heuristic principles lead to different historical paths of theoretic development, one might wonder whether these different heuristic principles might as well lead to different final destinations, that is to say to different, so to speak, 'final' theories of cancer. Such a consideration would lead to embrace a contingentist view of theories within which the particular phrasings of theories contain frozen historical elements of contingency. Following this line of thought, the first working hypotheses of a theory under development might determine the 'final' structure of the very theory itself. Therefore, the fact that the SMT and the TOFT are different could be more than a temporary divergence of scientific formulation: it could indeed be the early indication of a different 'final' theoretical formulation. Of course, at this point in time, such line of thought is purely speculative. Yet the future development, or not, of two parallel theories capable of explaining cancer at length yet incommensurable to one another, might help shed light on this topic.

4. Epistemological divide: theoretic and explanation (ir)reducibility

Epistemologically, the general question of organicism/reductionism translates into the question whether theories and explanations formulated in one field of science can be shown to be special cases of theories and explanations formulated in another field. The claim that carcinogenesis could be reduced to molecular biology would entail that theories and explanations of cancer could be reformulated as special cases of molecular biology, and thereby solely by reference to genes and molecular entities. To further clarify the debate between the SMT and TOFT proponents, we will make the distinction between two closely-related concepts of epistemological reduction, namely 'inter-theoretic reduction' and 'explanation reduction': whereas the first type bears upon formulations of theories and as such imposes quite heavy formal constraints, the second one appeals to the notion of explanation and allows more room for interpretation.

An 'inter-theoretic reduction' entails the availability of at least two formalized theories: the reducing theory for one, and the reduced theory for the other. Following the inter-theoretic framework proposed by Nagel (1961), the formalization process should take the form of an axiomatization in a formal language identical to the first-order predicate logic with identity; based on this formalization, the well-known conditions for a successful inter-theoretic reduction are conditions of connectivity (terms of the reduced theory must be connected to terms of the reducing theory), and of logical deducibility

(theoretical propositions of the reduced theory must be logically deducible from theoretical propositions of the reducing theory). Let us note that, in a midst of a prolific literature on the topic, such an 'inter-theoretic reduction' has been further extended, for instance, by Schaffner (1967) so as to encompass not only a syntactic view of scientific theories, but also a semantic view as well as cases of succession and replacement of theories. For the purpose of our discussion, it remains that, in any case, an inter-theoretic reduction entails an axiomatization of both the reducing and the reduced theory, as well as connectivity and derivability conditions. Applying the 'inter-theoretic reduction' scheme to carcinogenesis would mean that (1) at least two sets of theories should be available under an axiomatized form – a theory of cancer development on the one hand and a theory of genetics and molecular biology on the other – and (2) connectivity and derivability conditions should be fulfilled. Yet, these criteria are far from being met as of today: being research in progress and continuously appended, the current cancer theories are not under an axiomatized form, and for similar reasons nor are genetics and molecular biology, nor relevant subsets of these. Consequently, having no theoretical terms to connect nor properly axiomatized theories to derive, it is also not surprising that the conditions of connectivity and derivability would not be met. The debate on organicism/reductionism in cancer research would therefore seem quite premature if it were to be understood as an inter-theoretic reduction issue.

An alternative would therefore be to phrase the debate in terms of 'explanation reduction'. In this case, it would not be theories that one would like to reduce to one another, but explanations: if all explanations formulated in one field of science would be shown to be special cases of explanations formulated in another field together with structural information, than the first field would be 'explanatorily reduced' to the second field.[3] The organicism/reductionism debate in carcinogenesis is most likely grounded in this second type of reduction, focusing more on explanations than on theories as the proper locus of reduction, as would tend to confirm this quotation from Soto and Sonnenschein: "by [reductionism] we mean that explanations are sought for at the lowest possible level of organization, so that biology can eventually be reduced to chemistry and physics. […] In practice, this reductive thrust goes as far down as needed to construct an explanation" (2005, 104). In this context, what therefore remains to be clarified is the concept of explanation and its usage within the organicist/reductionist debate.

For this matter, let us suppose that we have an explanation E_1 of a carcinogenesis phenomenon by the SMT, and an explanation E_2 of the same phenomenon by the TOFT. Let us suppose furthermore that E_1 is an explanation that can be reformulated by appealing solely to explanations formulated in molecular biology, chemistry or physics (lower levels), whereas E_2 contains explanatory elements that cannot be reformulated in this same manner. In this situation, E_1 would be 'explanatorily *reducible*' and not E_2. Let us remark that this situation presupposes also that E_1 as well as E_2 are indeed *good*

[3] A weaker formulation of this reduction would focus solely on single explanations (and not on all explanations formulated in a particular field of science). In this case, the reduction would occur between explanations (and not between fields of science): if an explanation is shown to be a special case of another explanation, then the first explanation could be said to be reduced to the second one in the weaker sense of 'explanation reduction'.

explanations of carcinogenesis, which would mean, according to a pragmatist view of explanation (van Fraassen 1980), that these explanations would not only have a good probability to be *true*, but also that they would have an important weight compared to others in the *contrast class* (i.e. when answering a particular question rather than another one) and that they would in addition bear strong *contextual relevance* (i.e. when taking into account the contextual background of the one asking the question).

Now, if we go back to the debate on carcinogenesis, it appears that many criticisms formulated by proponents of the TOFT about the SMT are, in reality, much more targeted at the 'trueness' of explanations. Soto and Sonnenschein develop several paradoxes faced by the SMT: for instance, they mention the fact that the SMT has yet to provide an account for carcinogenesis cases involving multiple gene mutations as well as different orders of appearance of these mutations (2005, 106-110). Such criticisms are indeed showing that the SMT cannot provide a good explanation in the sense of failing to provide an explanation E_1 having a *good probability to be true*. Yet, if a theory cannot put forward a good explanation, it is in turn pointless to ask whether it can formulate a *reducible* explanation. This simply is the trait of a 'work-in-progress theory', and on this aspect, both the SMT and the TOFT are most likely to be put in the same basket since there appear to be phenomena that none of them can explain as of today.

To go further on this argument, we need therefore to take for granted the 'trueness' of E_1 and E_2, i.e. to suppose that both E_1 and E_2 have a good probability to be true. In this context, TOFT proponents would have a case if indeed the reducible explanation E_1 put forward by SMT proponents were still shown not to be a good explanation whereas their own explanation E_2 would actually be good. This could be the case if for instance E_1 would target the wrong element in the contrast class or miss contextual relevance.[4] Yet, should such a situation be exhibited, would this be problematic for reductionists? Most certainly not as this appears to be illustrative of the type of antireductionism that Rosenberg and Kaplan, for instance, define as epistemic antireductionism: "epistemic antireductionism begins with reasonable assumptions about the presuppositions, interests, cognitive characteristics, and background knowledge of informed inquirers, in this case,

[4] To illustrate this possibility, one could imagine the following fictitious scenario:

(A) E_1 and E_2 are true explanations of "why Paul got cancer",

(B) E_1 appeals to molecules (e.g. molecular expression), E_2 to tissue characteristics (e.g. wound),

(C) The contrast class more specifically highlights "what was specific about Paul history that made him get cancer",

(D) While it is known that "Paul was wounded and later a cancer grew at the very place of the wound".

In this case, E_2 is a better explanation than E_1 since it fits perfectly well the contrast class (C) and the relevance context (D).

On the other hand, one could imagine also that:

(C') The contrast class more specifically highlights "how is it that Paul's wound led to cancer?"

In this alternative scenario, explanation E_1 would be the better one since it would describe the molecular mechanisms at stake and how, for instance, a wound could impact the molecular expression of certain genes and thereby lead to cancer.

In this fictitious scenario, we see the possibility for the would-be TOFT explanation E_2 to be a good explanation whereas the SMT explanation E_1 would not be good or the other way around: the difference simply comes from the explanatory contrast class and the relevance context.

biologists. It holds that in the light of these assumptions, for these inquirers' questions, non-molecular, biological answers are adequately explanatory, and need no completion or correction by information from molecular biology" (2005, 44). In short, what matters is the adequacy of the explanation to the cognitive interest of the investigator. With this view of explanation, epistemic antireductionism is no surprise. This is a view that reductionists can easily embrace, for epistemic antireductionism can be hold by reductionists to reflect the temporary limits of our knowledge as well as the limitations of our cognitive capacities and the particular interests we have in framing questions.

In our view therefore, the core of the problem of explanatory reduction in carcinogenesis has often been misled for a problem of providing a *good* explanation, meaning either a *true* explanation (in the sense of 'having a good probability to be true') or an *appropriate* explanation (in the sense of fitting the contrast class and the relevance context), as exemplified by the criticisms of the SMT from proponents of the TOFT. We propose that a more appropriate strategy should instead be for the TOFT proponents to exhibit an E_2, that would be not only *good*, but also indeed *non explanatorily reducible*, i.e. that could not be reformulated by appealing to explanations formulated in molecular biology, chemistry or physics (lower levels) whatever proponents of the SMT might try. To our knowledge, such an example of explanation E_2 remains to be exhibited, as well as the impossibility proof to reformulate it in molecular biology, chemistry or physics together with structural information.

5. Organicism and ontological implications

Beyond methodological and epistemological aspects of reductionism, the organicist/reductionist debate in carcinogenesis sometimes ventures in the territories of ontological claims, as is the case with consequences of the organicist stance with respect to emergence and downward causation. Indeed, the organicist view adopted by Soto and Sonnenschein acknowledges and accepts "the existence of emergent phenomena" (Soto and Sonnenschein 2005, 104). The question that immediately follows is of course: which kind of emergence is at stake here and what are the phenomena exhibiting this emergence? Emergence has been and still is a mater of much debate among philosophers of science. Various concepts of emergence have been developed, weaker versions being compatible with a reductionist view while stronger versions not. Stephan (1999) for instance distinguishes six varieties of emergence. Among these six versions, three stand out as major options: weak emergence, synchronic emergence and diachronic structure emergence, all of these versions positing physical monism (i.e. entities classified as emergent are instantiated by systems consisting solely of physical parts) as well as synchronic determination (i.e. the fact that there can be no difference in the systemic properties without there being differences in the properties of the parts or their arrangements).[5] Let us recall briefly these three major options.

[5] The other three versions can be considered as variants of these three major ones and are not of central interest to our discussion: in addition to weak emergence, synchronic emergence and diachronic structure emergence, Stephan identifies weak diachronic emergence, strong diachronic emergence and strong

Weak emergence is the thesis according to which emergent properties are *systemic properties*, i.e. properties possessed by the system but by no part of it. Examples of weakly emergent properties are therefore properties such as 'walking', 'reproducing', 'having a sensation of pain'. They are typically opposed to so-called hereditary properties, i.e. properties possessed by the system itself and, as well, by some or all of its parts; such hereditary properties include for instance 'having a velocity'. Weak emergentism is compatible with contemporary reductionist approaches. The second perspective is the one of *synchronic emergentism* which central thesis is the *irreducibility* of properties of the system. As defined by Stephan, "a systemic property is irreducible if (a) it is neither micro- nor macro-scopically behaviorally analyzable, or if (b) the specific behavior of the system's components, over which the systemic property supervenes, does not follow from the components' behavior in isolation or in other (simpler) constellations" (1999, 52-53). Whereas the unanalyzability criterion refers to secondary qualities and phenomenal qualities such as colors or smells and induces no specific causal consequence, the second criterion appears to imply a challenging case of 'downward causation'. Indeed, since knowledge of the components' behavior – in isolation or in other constellations – is not enough to deduce the behavior of the system, and since within physicalism one cannot appeal to other external factors, then there must be some causal influence from the system itself onto its components. *Diachronic structure emergence* is the third major variant of emergence that Stephan identifies. Two features best characterize it: *novelty* and *unpredictability*. In this case, properties are emergent if they are genuinely novel in the sense that they appear for the first time, and unpredictable in the sense that they are governed by laws attributed to deterministic chaos.

Going back to carcinogenesis, the emergence involved in the organicist view of Soto and Sonnenschein is such that investigations or "incursions into lower levels must be followed by a synthesis of how lower level phenomena bear upon upper level phenomena" (2005, 104), implying that lower level phenomena somehow rest upon upper level ones, at least to a certain extent, and that, incidentally, lower level phenomena are causally dependent on upper level ones. To support this claim, Soto and Sonnenschein do not offer any example from carcinogenesis yet borrow one from morphogenesis: it is a case in which the activation of a gene within a group of cells is triggered by an increase in pressure due to growth and expansion of another group of cells (Farge 2003).[6] Based on their interpretation of this example, Soto and Sonnenschein infer that emergence and downward causation should likely be included in the organicist stance; they specifically indicate that the explanative "causal chain, from a molecular event to physical stress inducing the next molecular event appears as an emergent […] acting as a downward cause" (2005, 115). In this case, the main criterion for appealing to emergence is not a matter of a systemic property that would be possessed by the tissues; it is therefore not a

diachronic structure emergence. Please refer to Stephan (1999) for more details.

[6] The example under consideration concerns the work of biologist Emmanuel Farge on how developmental gene expression can be mechanically regulated by morphogenetic movements. In his work, Farge demonstrates how the application of a mechanical force – or a pressure – upon certain surface cells of a *Drosophila* embryo induces the expression of the 'Twist gene' around the entire dorsal-ventral axis and results in the ventralization of the embryo (see Farge 2003; Brouzès and Farge 2004).

matter of weak emergence as defined by Stephan. On the other hand, the issues at stake are neither issues of novelty nor of unpredictability in principle; therefore the version of emergence under consideration here is not one of diachronic structure emergence either. Indeed, the key reason for appealing to emergence appears to be the need to account for downward causation, a typical trait characteristic of synchronic emergence.

Yet, to which extent can the phenomena and scientific experiments under consideration here be interpreted solely in terms of downward causation? Soto and Sonnenschein acknowledge that "there are many interactions that occur simultaneously to maintain the structure of a tissue; hence it is practically impossible to sort out cause and effect in a way that would precisely reveal whether emergents have true causal agency" (2005, 115). So then, why appeal to downward causation? Is upward causation simply not enough? Looking more deeply into the morphogenetic example borrowed by Soto and Sonnenschein to justify downward causation, one can indeed wonder whether the phenomena could not as well be interpreted in terms of regular upward causation. The issue as framed by Soto and Sonnenschein appears as if an upper level phenomenon (cell multiplication) induces a lower level phenomenon (gene expression). We argue that a different account could be made as follows: cell multiplication might be the result of a process of cell division that is itself orchestrated by the internal molecular machinery of each individual cell; the outcome of this machinery results in the more or less twofold increase of the number of cellular molecules, and therefore, roughly, a twofold increase of physical volume; yet, if the volume available to the cells is somehow constrained, the increase in volume induces an increase in pressure, hence potentially a change in cellular shape and in turn different concentration gradients within a cell, depending for instance on molecules local production and usage sites. It is then perfectly plausible to imagine that a change in concentration could affect the expression of a gene, which, after all is nothing more than the result of a complex chemical reaction. The complete causal account would therefore be: a lower level event (gene expression) causes another lower level event (gene and molecular duplication) which result in an upper level event (cell multiplication) as well as in a physical event (increase of volume); this physical event causes other physical events (increase in pressure, change in cellular shape) which in turn has a causal incidence on a lower level event (change in chemical gradients, impact on chemical kinetics and gene expression).[7]

On this account, a causal explanation can perfectly be formulated by using only lower level events (molecular interactions) and physical events (change in volume, pressure). Appeal to upper level events (cellular or tissue interactions or movements) is not required, and even if a 'downward causation explanation' were to be formulated, for instance stating that the gene expression (lower level event) is triggered by moving cells due to cell multiplication (upper level event), this would not be a problematic case of

[7] In a similar fashion, Rosenberg (2005) argues that the formation or mal-formation of a chick-limb can be accounted for simply by appealing to upward causation, whereas Kitcher (1984) had presented this example as a biological case of downward causation. Also, in cancer research, Jacks and Weinberg (2002) provide an 'upward causation compatible' interpretation of the specific work of Bissell *et al* initially formulated as a matter of tissue organization. Morange (2005) also believes that an upward-causation explanation of the example borrowed by Soto and Sonnenschein is fully possible.

downward causation since it would remain, as already shown, perfectly compatible with an 'upward causation explanation'. This would indeed remind us of the 'celadon vase' example of Kim (1999): the falling vase (upper level event) hits an air molecule and changes its momentum (lower level event). In this case the 'downward causation explanation' is perfectly reducible and non problematic: as Kim puts it, it is a case of 'non-reflexive downward causation'. Even Farge himself, who claims to be investigating "how morphogenetic movements could modulate the expression of developmental genes", believes that it is necessary to decipher the "underlying molecular mechanism of mechano-transcription" (2004, 367). Of course, we could imagine a slightly more complicated biological case with a kind of retroactive feedback: the upper level event (moving cells due to cell multiplication) would induce a lower level event (gene expression) which would in turn affect the upper level event (increase/decrease of cell multiplication rate). Would this be problematic? Most certainly not, as it would fit the case of 'diachronic reflexive downward causation' proposed by Kim, since events trigger one another in a sequential fashion. What would be more problematic would be an example of 'synchronic reflexive downward causation', even if Kim doubts that it could be given a coherent sense. Thus, although the organicist stance posits a synchronic type of emergentism and strongly advocates downward causation, the experimental evidence of such downward causation leaves the door open to another interpretation compatible with upward causation and reductionism. To our knowledge therefore, a real example of problematic downward causation of the synchronic reflexive type still remains to be exhibited in the case of carcinogenesis, like in many other areas of science.

6. Beyond an apparent incommensurability

Having shed light on the organicist/reductionist debate in carcinogenesis from the three different perspectives of methodology, epistemology and ontology, which lessons can we now learn? First, it appears that a strong divergence of approach does indeed concern heuristics and research strategy, especially as it has been pursued so far. Second, from an epistemological point of view, it appears that the debate is best understood as an issue of 'explanation reduction', but also that arguments on cancer explanations aim more at their 'trueness' and 'appropriateness' rather then their '(ir)reducibility'. Third, from an ontological point of view, we contend that the synchronic emergence entailed by the organicist stance is not tenable, or at least not in the form it is proposed. In our view therefore, the three-tiered analysis of the organicist/reductionist debate in carcinogenesis shows that the gap between the two approaches is not as wide and clear-cut as might first have seemed.

Is this gap enough then to argue for a fundamental incompatibility of both theories to a point of incommensurability as suggested by Soto and Sonnenschein (2005, 114)? If one sticks to a very strict and restrictive formulation of each theory, that is, if we take the SMT as a theory looking solely for genetic causes of cancer and the TOFT as a theory investigating solely tissue organization causes of cancer, then the two theories may well appear incommensurable for they would appeal to mutually incompatible explanations and causal factors: all laws of the SMT would only be formulated in terms of genes and

molecules, notions absent from the TOFT; on the other hand, all laws of the TOFT would appeal to tissues and tissue organization, terms which do not exist in the SMT. Yet, we argue that one cannot stick to such strict formulations of both carcinogenesis theories, and for two reasons.

First, both the SMT and the TOFT are theories in progress. Everyday, cancer still kills and, as a matter of fact, none of these two theories can stand out and claim to provide a complete explanatory framework for carcinogenesis. One could even question their naming as theories: as such, both the SMT and the TOFT are incomplete candidate explanations for carcinogenesis; they are hypotheses being continuously reworked and submitted to experimental test and refutation; their formalism is continuously adapting to new experimental evidence, making it impossible to stick to such a precise formulation.

Second, as new research pathways are investigated, one can wonder whether the two theories will indeed remain in their initial narrow explanatory realms or whether they might each help to shed a different light on the same issue, and thereby converge. Recent evidence would point in this last direction. Indeed, not only are the two theories expanding outside of their initial starting paradigms, they are also starting to collide and overlap at their periphery. Weinberg for instance no longer points at a unique tumor cell for cancer explanation; rather, he acknowledges the importance of the interactions between tumor cells and their neighboring normal cells in carcinogenesis: "cancer development depends upon changes in the heterotypic interactions between incipient tumor cells and their normal neighbors" (Hanahan and Weinberg 2000, 67). Moreover, the SMT appears to recognize the importance of interactions between epithelial cells and the stroma (Jacks and Weinberg 2002), and starts to make sense, at the molecular level, of cell-to-cell interactions within tissues (Orimo *et al*, 2005). On the other hand, after having assessed the role of tissue organization in carcinogenesis, the TOFT needs to dive into the search for some molecular explanations: Soto and Sonnenschein recognize that, since altered communication among cells is at the core of the TOFT, "one would study how specific alterations in APC, catenins, cadherins and hDd affect the development of intestinal crypt and give rise to polyps" (Soto and Sonnenschein 2005, 114). Hence, as a matter of fact, the TOFT needs to expand its explanatory paradigm from the level of tissue organization down to the level of molecules involved in cell-to-cell interactions, while the SMT is looking beyond the cell and the faulty gene to cell-to-cell interactions within tissues. Therefore, both the SMT and the TOFT are currently colliding on some common ground and could very well be heading in the same direction in the future. It even appears that a number of research papers on carcinogenesis could be interpreted as attempts at formulating synthetic positions that would incorporate claims from both theoretical approaches or at least build bridges between the two initial paradigms (for instance, to name a few: Folkman *et al.*, 2000; Bissell and Radisky, 2001; Thiery, 2002; Wiseman and Werb, 2002, Jacks and Weinberg 2002). This could the sign of a trend towards a unification of both theories into a larger cancer theory, involving the genetic circuitry within cells as well as the organizational patterns of cells within tissues and their molecular interactions. It might also be the sign of another change in cancer research, going along the pathways of 'systems biology'.

Indeed, the ever-growing extraordinary complexity of factors uncovered so far seems to be pointing at multiple and intricate pathways for carcinogenesis: Han and Weinberg indicate for instance that the recent application of transcriptional profiling to cancer has documented changes in the expression of *thousands* of genes as normal cells undergo transformation into their neoplastic derivatives (Han and Weinberg, 2002). This is potentially shifting the focus from 'which entities – molecules, tissues – cause cancer?' to 'how are all cancer-involved entities related to one another and how are these relationships disrupted in the case of cancer?'. Reflecting on this general recent trend in biology, Keller (2005) suggests that the move towards 'systems biology' be accompanied by a change of conceptual framework resting on a dynamic and relational epistemology. Morange (2005) is also emphasizing the role of such new explanatory schemes and their articulation with more traditional explanatory schemes of biology. As more and more detailed investigations are carried out, very complex arrays of explanatory factors are uncovered, involving ever-increasing numbers of entities appearing to be organized in complex causal relationships. The uncovering of numerous interactions, including retroactive non-linear ones, across many levels of biological information calls for studying with a 'systems approach' how these interactions simultaneously work together. Within this change of conceptual framework, explanations can no longer be framed in terms of genes, cells or tissues; rather, they are formulated in terms of multitudes of complex interactions among entities potentially pertaining to different biological levels and in ways that are familiar to computer science or to the science of complex systems. What we contend here is that the study of carcinogenesis may very well be heading in the same direction. If this is so, cancer theories will shift their focus from looking at specific entities, be they molecules or tissues, to picturing complex networks of interactions. Explanations will no longer be framed in terms of faulty genes, malignant cells or tissue disorganization: they will depict an ever more accurate model of extremely complex and interacting processes potentially ranging across several levels of relevant biological information, including physico-chemical variables if needed.

Yet, once cancer theory has shifted to a 'systems biology' framework, what will happen to the initial problem of organicism/reductionism? From an epistemic point of view in particular, will the explanations put forward within a 'systems biology cancer theory' be reducible to molecular and physico-chemical explanations? O'Malley and Dupré (2005) view 'systems biology' as mainly composed of two research streams: a 'pragmatic systems biology' emphasizing large-scale molecular interactions and compatible with physico-chemical reductionism, and a 'systems-theoretic biology' emphasizing system principles and viewing them as synchronically emergent top-down constraints. Which stream will best characterize future cancer research? This is an open question that can only be answered by scientists. And the answer may, or may not, lead to the reappearance of emergentist questions. Yet this time such questions would not be framed in terms of biological levels (tissues, cells) but in terms of systemic properties (design principles) if any.

We also propose that another type of emergentist questions might rise from a diachronic perspective shed on complex systems. For instance, this is typically the case for cellular automata, and this has led Bedau among others to propose a form of

diachronic structure emergence (Bedau 1997).[8] What could bring, in the future, some support to the TOFT line of argumentation would be to show that the complete explanation of carcinogenesis would not only be a typical example of complex biological systems modeling, but would also imbed formal models exhibiting diachronic structure emergence, i.e. a form of computational incompressibility. In this case, emergence could percolate from models of complex systems into carcinogenesis explanations. Yet, opposite to Soto and Sonnenschein claim, this would not be a case of synchronic emergence entailing an ontological claim of downward causation.

7. Conclusion

As we have seen, the study of carcinogenesis has become the ground of a passionate debate between researchers not only interested in the progress of their scientific investigations *per se* but also reflecting on their own epistemological stances. The opposing stances of reductionism and organicism as used in cancer research have been discussed along three dimensions – methodological, epistemological and ontological – so as to clarify arguments used by both sides and measure the actual gap between the two stances. We therefore contend that the major difference between the two stances is best stated in terms of diverging heuristics whereas claims of explanation (ir)reducibility do not appear convincingly stated; in addition, we argue that the synchronic emergentist view of the organicist stance and its implications in terms of downward causation appear too ontologically loaded. As time is passing by, we witness a trend towards a convergence of explanations in cancer research: bridges are tentatively built between approaches, and 'candidate theories' are constantly reformulated to accommodate new experimental evidence. In addition, as the field of carcinogenesis is enriched and enlarged, thereby becoming of an ever more tantalizing complexity, similar changes in the biological sciences calling for a new 'systems biology' might as well impact the way cancer theories are formulated; with such a change of conceptual framework, the two current candidate theories for carcinogenesis, the SMT as well as the TOFT, might very well leave way to a third candidate theory, a 'systemic approach to carcinogenesis'. Time will tell. This approach might however enable two other forms of emergence to percolate back into carcinogenesis: a synchronic emergence relative to system constraining principles, and a diachronic structure emergence relative to computational incompressibility. The question is open to scientific investigation.

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[8] Bedau studies cellular automata and in particular Conway's "game of life" (Bedau 1997); he calls 'weak emergence' the form of diachronic emergence exhibited by such models of complex systems. To avoid confusion with Stephan's typology of emergence (Stephan 1999), we prefer to use 'diachronic structure emergence' in this case.

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References

Ayala, F.J. 1974. Introduction. In Ayala F.J. and T. Dobzhansky (eds) *Studies in the philosophy of biology. Reductionism and related problems*. London: McMillan : vii-xix.

Bedau, M. 1997. Weak Emergence. *Philosophical Perspectives: Mind, Causation, and World*, 11: 375-399, Malden MA.: Blackwell.

Bissell, M.J. and D. Radisky. 2001. Putting tumors in context. *Nature Reviews Cancer* 1: 46-54.

Boveri, T. 1914. *Zur Frage der Entstehung Maligner Tumoren.* Jena: Fischer.

Brouzès, E. and E. Farge. 2004. Interplay of mechanical deformation and patterned gene expression in developing embryos. *Current Opinion in Genetics & Development* 14: 367–374.

Dolberg, D.S and M.J. Bissell. 1984. Inability of Rous sarcoma virus to cause sarcomas in the avian embryo. *Nature* 309: 552-556

Farge E. 2003. Mechanical induction of twist in the *Drosophila* foregut/stomodeal primordium. *Current Biology* 13:1365-1377.

Folkman, J., P. Hahnfeld, L. Hlatky. 2000. Cancer: looking outside the genome. *Nature Reviews Molecular Cell Biology* 1: 76-79

Han, C.W. and R.A. Weinberg. 2002. Modeling the molecular circuitry of cancer, *Nature Reviews Cancer* 2: 331-342.

Hanahan, D. and R.A. Weinberg. 2000. The hallmarks of cancer, *Cell* 100: 57-70.

Jacks, T. and R.A. Weinberg. 2002. Taking the study of cancer cell survival to a new dimension, *Cell* 111: 923-925.

Khayat D. 2005. Nous allons changer la culture de la recherche sur le cancer, *Le Monde*, 23 May 2005.

Keller, E.F. 2005. The century beyond the gene, *Journal of Biosciences* 30(1): 3-10.

Kim, J. 1999. Making sense of emergence, *Philosophical Studies* 95: 3-36.

Kitcher, P. 1984. 1953 and all that, *Philosophical Review* 93: 335-373.

Maffini, M.V., A.M. Soto, J.M. Calabro, A.A. Ucci, C. Sonnenschein. 2004. The stroma as a crucial target in rat mammary gland carcinogenesis, *Journal of Cell Science* 117: 1495-1502.

Marcum, J.A. 2005. Metaphysical presuppositions and scientific practices: reductionism and organicism in cancer research, *International Studies in the Philosophy of Science* 19: 31-45.

Morange, M. 1997. From the Regulatory Vision of Cancer to the Oncogene Paradigm, 1975–1985, *Journal of the History of Biology* 30: 1–29.

Morange, M. 2005. *Les secrets du vivant. Contre la pensée unique en biologie*, Paris: La Découverte.

Needham, J. 1936. New advances in chemistry and biology of organized growth, *Proceedings of the Royal Society of Biology* 29:1577–1626.

Orimo, A., P.B. Gupta, D.C. Sgroi, F. Arenzana-Seisdedos, T. Delaunay, R. Naeem, V.J. Carey, A.L. Richardson, R.A. Weinberg. 2005. Stromal Fibroblasts Present in Invasive Human Breast Carcinomas Promote Tumor Growth and Angiogenesis through Elevated SDF-1/CXCL12 Secretion, *Cell* 121: 335-348.

O'Malley, M. and Dupré, J. 2005. Fundamental issues in systems biology, *BioEssays*, 27:1270-1276.

Nagel, E. 1961. *The Structure of Science. Problems in the logic of scientific explanation.* New York: Harcourt, Brace & World.

Rosenberg, A. and D.M. Kaplan. 2005. How to reconcile physicalism and antireductionism about biology. *Philosophy of Science* 72: 43-68.

Schaffner, K. 1967. Approaches to reduction. *Philosophy of science* 34(2): 137-147.

Sonnenschein, C. and A. Soto. 1999. *The Society of Cells: Cancer and Control of Cell Proliferation.* New York: Springer Verlag.

Sonnenschein, C. and A. Soto. 2000. The somatic mutation theory of carcinogenesis: why it should be dropped and replaced. *Molecular Carcinogenesis* 29: 1-7.

Soto, A. and C. Sonnenschein. 2004. The somatic mutation theory of cancer: growing problems with the paradigm? *BioEssays* 26: 1097-1107.

Soto, A. and C. Sonnenschein. 2005. Emergentism as a default: cancer as a problem of tissue organization, *Journal of Biosciences* 30(1): 103-118.

Stephan, A. 1999. Varieties of emergentism, *Evolution and Cognition* 5(1): 49-59.

Thiery, J.P. 2002. Epithelial-mesenchymal transitions in tumour progression. *Nature Reviews Cancer* 2: 442-454.

Van Fraassen, B. C. 1980. *The Scientific Image*. Oxford: Clarendon Press

Van Helvoort, T. 1999. A century of research into the cause of cancer: is the new oncogene paradigm revolutionary? *History and Philosophy of the Life Sciences* 21(3): 293-330

Waddington, C.H. 1935. Cancer and the theory of organizers, *Nature (London)* 135:606–608.

Weinberg, R.A. 1998 *One Renegade Cell: How Cancer Begins*. New York: Basic Books

Wiseman, B.S. and Z. Werb. 2002. Stromal effects on mammary gland development and breast cancer. *Science* 296: 1046-1049.