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Abstract

Two main theories aim at understanding carcinogenesis: the reductionist SMT locates cancer in cancer cells, while the organicist TOFT locates cancer at the tissue level. For TOFT, the 'cancer cell' is a phlogiston, SMT is an old paradigm which ought to be replaced. Recently two critics have argued that TOFT and SMT, despite their apparent strong incompatibilities, are actually compatible. Here we review their arguments. We show that these arguments are based on interpretation mistakes that become understandable once one grants that criticizing a paradigm from the point of view of another, in which words do not have the same signification, bears the risk of strong misunderstandings. These misunderstandings, in our experience, are common. We hope that this discussion will help clarifying the differences between TOFT and SMT.

Keywords: TOFT, reductionism, organicism, levels; SMT

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1. Introduction

Two main theories strive to explain carcinogenesis: the Somatic Mutation Theory (SMT), and the Tissue Organization Field Theory (TOFT). SMT adopts a reductionist stance and fundamentally attributes cancer to genetic defects in cells. It has dominated the field of cancer biology for the past 50 years but has met difficulties, both in terms of empirical evidence and lack of medical impact, so that one of its main proponents mourns that after a period of "reductionist triumphalism" we are now back to "endless complexity" (Weinberg, 2014, p. 267). TOFT, by contrast, adopts an organicist stance, and postulates that cancer is primarily tissue disorganization (Sonnenschein and Soto, 1999).

According to its proponents, it has met notable empirical success (Baker, 2011).

Two critics have recently aimed at showing that SMT and TOFT are actually compatible, and both reductionist (Bedessem and Ruphy, 2015, 2016). The claim, at first, is surprising, since it contradicts the declarations of the very authors of TOFT.

Philosophical papers, however, can be wrong, like experimental papers, for methodological reasons. The two critics, as we will see, failed to cite the relevant literature, miscited the literature cited, and misrepresented basic concepts in TOFT. They grounded their account on a criticism of Marcum's (2009) account of scientific reduction, an account which is held neither by the tenants of TOFT nor by many philosophers of science. Crucial to their argument was their assumption that "tissues are considered as an ensemble of cells" (2015, 263), an assumption which is held neither by the tenants of TOFT nor, to our knowledge, by any biologist.

We first briefly introduce TOFT and SMT. We then critically review the arguments of the critics. We argue that their mistakes are not fortuitous but can be interpreted as an illustration of the strong divergence between the SMT and TOFT paradigms. Our aim here is not to argue for TOFT, but for a precise characterization of TOFT. Whatever the future of cancer biology holds, understanding the originality of TOFT is a prerequisite to assessing its theoretical and experimental fruitfulness.

2. SMT and TOFT: a brief introduction

2.1 SMT: the cell as the focus

The Somatic Mutation Theory of cancer traces back to the beginning of the XXth century and has progressively mutated to become the dominant view in the past 50 years (Boveri, 1914; Soto and Sonnenschein, 2014).[1] SMT states, in a nutshell, that cancer is a cell-based disease driven by somatic DNA alterations which increase cell proliferation (Hanahan and Weinberg, 2000). Accordingly, most carcinogens are assumed to be so in virtue of being mutagenic.

At the core of carcinogenesis is the appearance of 'cancer cells'. These cancer cells are assumed to be the product of several successive mutations (on oncogenes, tumor suppressor genes, DNA repair genes, etc.) which, supposedly, make these cells proliferate more, leading to their higher fitness (in the population genetics sense).[2] Normal cells are assumed to be quiescent by default and to require 'signals' in order to proliferate.[3] Cancer cells do not. As a result, cancer is assumed to be a (problematic) self-sustained cell proliferation.

It follows that the main therapeutic strategy stemming from the SMT is to target these cancer cells and kill them selectively. This strategy is facing a crisis due to its limited medical outcomes (Lichtenberg, 2010; Godlee, 2016).

SMT is thus centred at the cellular level. It professes a reductionist stance. It combines molecular and cell biology, to seek for molecular alterations mediating carcinogenesis, and a population genetics rationale to justify the amplification of single cell defects.

2.2 TOFT: the tissue as a focus

The Tissue Organization Field Theory has been proposed by Sonnenschein and Soto (1999). It takes place in a broader stream of works questioning the level at which cancer takes place.[4] TOFT states that cancer is essentially a developmental disease, occurring at the level of the tissue. Carcinogenesis is understood as a disorganization of the morphogenetic field of the tissue.[5]

In TOFT, the default state of the cell is proliferation with variation and motility. Healthy tissues impose constraints on cell proliferation (via mechanical forces, chemical inhibitors, etc.).[6] However, a disruption of tissue organization can release those constraints, resulting in cell proliferation with variation and motility, and in further disorganization of the tissue. Carcinogens are assumed to be so in virtue of altering the tissue architecture (e.g. asbestos), or of interfering with development (e.g. endocrine disruptors).

Cancer occurs at the tissue level, with phenomena such as dysplasia and metaplasia. The appearance of carcinoma (epithelial cancer), for instance, fundamentally involves reciprocal interactions between the two main parts of the considered tissue, the epithelium which typically proliferates abnormally, and the stroma which surrounds the epithelium. Being a 'cancer cell' is not a genuine property of the cell: 'cancer cells' do not acquire new competences, and they can be normalized if placed in an appropriate tissue (this contradicts the population genetics view of SMT).

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1 SMT does not start neatly with two authors and it is possible that the current version be a 'phantom' scientific project (Wolfe, 2016), crystallized in reaction to TOFT (see also Coffman (2005); Soto and Sonnenschein (2005)). We give here an account which we deem faithful to the first 'Hallmarks' paper (Hanahan and Weinberg, 2000).

2 See e.g. Nowak, Michor and Iwasa (2003).

3 To be precise, the 'Hallmarks' paper is inconsistent on this question: "Normal cells require mitogenic growth signals (GS) *before they can move from a quiescent state* into an active proliferative state. … Within a normal tissue, multiple antiproliferative signals *operate to maintain cellular quiescence* and tissue homeostasis…" (pp. 58-60 Hanahan and Weinberg, 2000, our emphasis). In other terms, normal cells need signals both to be quiescent and not to be quiescent. A way out of this inconsistency is to consider that there is no defined default state in SMT. This latter interpretation shall not affect our argument, since SMT would still be incompatible with TOFT.

4 See for example Berenblum and Shubik (1949), Brinster (1974), Pierce et al (1974), Kenny and Bissell (2003), Bizzarri et al (2008), Barcellos-Hoff (2010). We thank a reviewer for suggesting these references to us.

5 Technically, organization should be understood here as the mutual dependencies between the parts of an organism, which can to an extent be proper to an individual (Montévil and Mossio, 2015). Cancer is then characterized by an increase of morphological complexity and a loss of organization (Longo et al, 2015).

6 Applications of this notion of default state can be found in Ginzburg and Colyvan (2004); Soto, Longo, Montévil and Sonnenschein (2016); Montévil, Speroni, Sonnenschein and Soto (2016). Montévil et al. (2016) also discusses the default state used in several mathematical models of mammary gland morphogenesis.

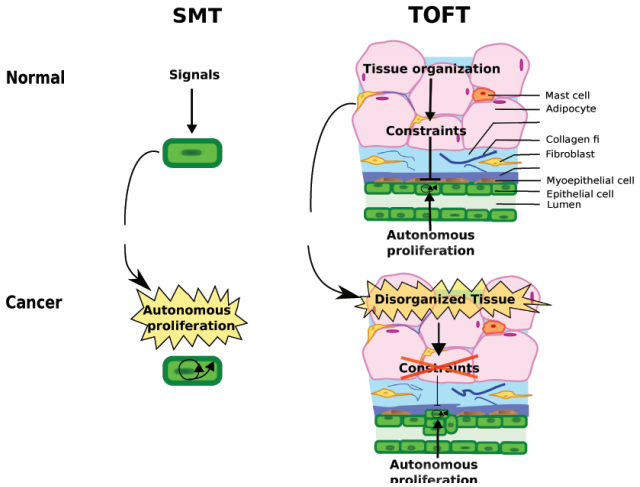

Figure 1. *Tissue stability and carcinogenesis in SMT and TOFT, the example of mammary glands*. In SMT (left), normal epithelial cells are quiescent by default: this state does not require an explanation (but see footnote 3). Carcinogenesis is then a process in which a series of mutations leads to the advent of cancer cells that proliferate and move spontaneously. In TOFT (right), normal tissue constrains the proliferation and motility of cells, leading to tissue homeostasis. Carcinogenesis is characterized by a disruption of the normal tissue organization that leads to the loss of these constraints and to abnormal proliferation, cell movements and further abnormal tissue architecture. The above schematics are highly simplified for representation purpose. For TOFT, we focus on the effect of constraints on a single epithelial cell to lighten the representation.

TOFT thus finds its home in developmental biology. It adopts an organicist perspective where the tissue is the focal level, at the crossroad of both bottom-up (e.g. cell and extra-cellular matrix to tissue) and top-down approaches (e.g. organism to tissues).

2.3 Reductionism and organicism

At this point, the reductionist reader might wonder how a whole can have properties, which are irreducible to properties of its parts, as do tissues in TOFT.

To show this, we shall consider a balloon as a toy example. The balloon is, topologically, a sphere. The topology of the balloon is not, obviously, a property of one single rubber molecule. But an immediate temptation is to reduce the topology of the balloon to the individual positions of all the rubber molecules. Yet, these individual positions are insufficient: what is lacking is, precisely, the topological relationships between the molecules, their neighbourhoods, their connections, so to speak. More precisely, the topology of the balloon is a property of the possible transformations of the shape of the balloon: whether it is stretched or bumped, inflated or soft, as long as we make no hole in it, its topology remains the same. The topology of the balloon is a conserved property of the whole, which is not reducible to properties of the parts.[7]

Similarly, the organization of the tissue is not reducible to properties of parts of the tissue. The topological properties of an acinus, for instance, cannot be defined at a level lower than that of the acinus itself. Arguably, there is more to biology than conserved tissue-level properties such as topology (as we and colleagues have argued in Montévil et al, 2016), but there is hardly less.

Now, TOFT is also more than just non-reductionist: it is organicist. We cannot do better to explain organicism than to recall a passage by Gilbert and Sarkar (the importance of the quote will soon become obvious):

> [R]eductionism [can be pictured] as a system where a "bottom-up" approach (e.g., atoms to molecules to organelles to cells to tissues) is sufficient to explain all phenomena. Organicism claims that this is not sufficient and that top-down and bottom-up approaches must both be used to explain phenomena. For instance, reductionist ontology and explanations would see a tissue as an organized collection of cells and cells as an organized collection of organelles, etc. Organicist ontology and explanations would include those bottom-up considerations but would also include the functioning of the tissue within the organism, the functioning of the organism within its environment (and, perhaps, other parameters as well). The structure and function of a hepatocyte depends not only on the properties of organelles comprising it, but also on the properties of the organ in which it resides. (Gilbert and Sarkar, 2000, p. 2)

In TOFT, 'organization' thus includes bottom-up and top-down relations. It is "a dynamic state of interdependence of levels that includes both structures and functions as well as integration and regulation" (Longo et al., 2015, p. 965).

2.4 Relationships between SMT and TOFT

Roughly speaking, for SMT, cancer is in the cell; for TOFT, cells are in the cancer. In Table 1, we gather the various core aspects of SMT and TOFT discussed in the previous section.

An immediate temptation – which we have encountered several times in discussions with colleagues external to TOFT, and which is advocated by the critics we respond to here – is to say that SMT and TOFT provide

[7] Another example is in thermodynamics. Thermodynamic phenomena are oriented in the sense that some thermodynamic processes are irreversible. However, the trajectory of every single molecule is reversible in classical mechanics. Irreversibility is a property of the system and not of the elements. A century of hard mathematical work and the edification of non-trivial hypotheses have been necessary to articulate the two levels. [See for example Chibbaro, Rondoni and Vulpiani (2014), Bitbol (2012), Longo, Montévil and Pocheville (2012), and Longo and Montévil (2014)].

alternative, compatible causal pathways targeting the same domain of validity (cancer). In this sense, genetic mutations and tissue disruption would be two pathways to obtain the same phenomenon, as would for instance different forces in Newtonian mechanics. The coexistence of different forces in Newtonian mechanics, however, does not lead to a logical inconsistency. We consider that a close examination of TOFT reveals differences with respect to SMT, which lead to the conclusion that they are actually logically incompatible (in particular because TOFT supposes a default state of proliferation, which SMT does not). The coexistence of SMT explanations and TOFT explanations targeting a single phenomenon is thus not as straightforward as it seems.

The question of the incompatibility between SMT and TOFT is, of course, orthogonal to that of their respective validity. For instance, quantum mechanics and general relativity are logically incompatible, but they both have their domain of validity, and issues only appear in the small overlap of these domains. SMT, for instance, could be valid for some cancers (say, 'cell cancers') and TOFT for others (say 'tissue cancers'). The two theories can also be speculatively mutated to incorporate elements of the other while retaining their core assumptions (i.e. cell/tissue as for the level, quiescence/proliferation as for the default state). SMT can be extended to include an effect on gene regulation by the cellular microenvironment (Hanahan and Weinberg, 2011) – though not by the tissue, which is not a proper level of action in this scheme. TOFT might be extended by considering that somatic mutations can play a role in relieving constraints stemming from the tissue, if they can affect the whole organization field.

Finally, the cores of both theories might be speculatively mutated to formulate a grand overarching theory of cancer (say, 'SMTOFT'), one where *tissues* would constrain cells but where the fact that cells can proliferate and move with *intrinsic, heritable, varying rates* by default would also play a key explanatory role (Capp, 2012; Rosenfeld, 2013).

Theories can be multiplied beyond necessity. Whether their multiplication or unification are timely and useful depends on how much one is able to articulate the alternative points of view and to approach critically empirical results. Premature unification, in particular, is at risk of leaving aside genuine changes of perspective brought by the youngest alternatives. In the next section, we give an example of critics falling, we think, into this trap.

3. Critics of TOFT: a detailed examination

Two critics have recently argued that SMT and TOFT are compatible and both reductionist (Bedessem and Ruphy, 2015, 2016). To do so, we will see that they had to give no role for the tissue organization field and none as well for theory in cancer biology. Hence, not much was left of the Tissue Organization Field Theory, the remains of which being then accommodated with SMT. We review here a sample of their mistakes. To facilitate reading, we add square-bracketed comments within the critics' quotes.

	SMT	**TOFT**
Cancer is:	Mutated cancer cells	Development gone awry
Default state of cells	Quiescence	Proliferation with variation and motility
Theoretical causes of cancer	Somatic mutations	Alterations of tissue organization
Manifestation of these causes	Proliferation and motility of cells	Removal of constraints on the default state
Location of cancer	Cancer cell	Tissue organization field
Paradigmatic terms	Growth factors, signals, information, oncogenes	Morphogenetic fields, constraints, agentivity
Reversibility of carcinogenesis	No	Yes
Main medical strategy	Kill cancer cells	Prevention, exploit cancer reversibility
Core associated field	Molecular/cell biology	Developmental biology
Attitude	Genetic reductionism	Organicism

Table 1. Comparison of SMT and TOFT

3.1 The importance of development

Surprisingly, the critics ended up talking about TOFT without mentioning development. However, TOFT considers cancer as a developmental disease where neoplasms are "development gone awry" (Soto, Maffini and Sonnenschein, 2007). The importance of development in cancer biology could be debated, but it is central to TOFT, including at the level of the experimental methods involved such as recombination experiments. An example of application is the analysis of endocrine disruptor as carcinogens (Soto and Sonnenschein, 2010).

3.2 The importance of biology

The interpretation of TOFT from a SMT point of view lead the critics to be biologically imprecise in several places. For instance:

> But according to TOFT, cancer is still located in individual cells **[This is false].** In particular, one of the theoretical basis of TOFT deals with the default state of the cell (proliferative or quiescent). This means that the advocates of TOFT *need to* consider that the cell is the fundamental unit of the organism **[This does not follow**[8]**]**. … More generally, according to TOFT, modifications of the molecular composition of the stroma cause cancer **[This is false]**. … SMT looks into the cell, by considering the structure of the DNA, and TOFT looks outside the cell **[This contradicts the first sentence]**, by considering the molecular relationships between *each cells* [sic] and the stroma **[This is false]**. (2015, p. 264, their emphasis)

In carcinoma, SMT looks inside epithelial cells: 'the cancer cells'. The other cells are not the main focus of investigation. TOFT instead focuses on the tissue level, and in particular on the relations between the epithelium and the stroma, and looks inside these components. The stroma includes cells, such as fibroblasts, macrophages, adipocytes, and all of them play an important role. The critics do not specify which cells they talk about and seem to confuse the stroma and the cellular micro-environment or maybe the extra-cellular matrix.

3.3 The importance of theory

The critics adopt the most deflationary possible position in the debate, seemingly forgetting that it is, for TOFT advocates such as Soto and Sonnenschein, all about theories:

> Their [Soto and Sonnenschein's] central idea is that the original cause of cancer is not genetic mutations, but disruption of tissue cohesion. (2015, p. 258)

The central idea of Soto and Sonnenschein is to propose a new theory of cancer. To them, briefly put, a theory is based on core assumptions, including a default state (Longo et al., 2015; Soto et al, 2016). Theories are conditions of possibility of explanations in that they define causal structures in which particular causes can then act (Sonnenschein and Soto, 2008). The central idea of Soto and Sonnenschein is certainly not to add yet another kind of cause to an otherwise poorly defined picture of cancer. This deflationary reading by the critics, who reduce a theory to a piece of mechanism, is a thread in their misunderstanding of the incompatibility between SMT and TOFT:

> Our suggestion is that, from a biological perspective, the two theories have to be thought as proposing two distinct, and compatible, *causal pathways* which can initiate and promote carcinogenesis. (2015, p. 264, their emphasis).

By contrast, as we argued above, a close reading of the TOFT literature rules out this interpretation. Similarly, the critics refuse to discuss the notion of default state (2016, p. 84), which is by contrast crucial to the view they criticize.[9] Eventually, this deflationary reading by the critics explains why they have so great troubles identifying TOFT authors in several places. (For instance they write on p. 258 of their 2015 paper that TOFT has been 'popularized' by Soto and Sonnenschein.)

3.4 The importance of the philosophical method

To argue for the non-anti-reductionism of TOFT, the critics implement the most improbable philosophical method: they criticize (with, we argue, mistakes) a somewhat confidential paper (Marcum, 2009)[10], never cited in TOFT[11] only because, apparently, this paper mentions TOFT:

> This definition [of organicism] is interesting since Marcum presents TOFT as an organicist theory. As a consequence, it is a way to investigate the coherence of this claim. (2015, p. 262)

It would have been more appropriate to start with the concepts of reductionism and organicism found in Gilbert and Sarkar (2000, quoted above), which is abundantly cited, in particular in TOFT. Deceived by their false start, the critics go on confusing two very different stances, organicism and (the most naïve possible) holism:

> In biology, *holism* translates into *organicism* … [In the holistic view], it is epistemologically useless to consider the smallest scales to study a given object. (2015, p. 262, their emphasis)

Unfortunately, the quote completely contrasts with a passage by Soto and Sonnenschein, already quoted

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[8] Actually, Soto and Sonnenschein advocate that there is a coupling between the level of the organism and the level of cells in development (Soto, Sonnenschein and Miquel, 2008).

[9] To be fair, the critics do cite Rosenfeld (2013) for this abdication, but Rosenfeld only explains that he does not understand the notion.

[10] The critics cite what seems to be another version of the same paper (Marcum, 2010), which we were not in a position to find.

[11] Bizzarri and Cucina (2016) do cite the paper, but they copy-pasted the reference from the critics. Another paper by the same author has been sometimes cited in the TOFT literature (Marcum, 2005).

from "we advocate" in the paper by Marcum (2009, p. 279) which the critics cite at length (see also e.g. Soto, Sonnenschein and Miquel (2008, p. 16)):

> *Neither Evelyn Fox-Keller, nor us 'advocate a holistic view'. Fox-Keller proposes 'explanatory pluralism' (Keller, 2002, p. 300), and we advocate a hierarchical view of biology that recognizes the existence of emergent phenomena and their causative powers. In this view* both top-down and bottom-up approaches are used *(Sonnenschein and Soto, 1999).* (Soto and Sonnenschein, 2005, p. 460, with modified citation format and our emphasis)

The critics then go on using Marcum's confidential and idiosyncratic account of reductionism (which they deem "classical", 2015, p. 264), to make the central point of their paper:

> J-A. Marcum defines three types of reductionism (Marcum, 2010). *Theoretical reductionism* aims at reducing the terms of a high-level theory to terms belonging to low-level theories. … *Ontological reductionism* deals with the description of the elementary components of natural objects or phenomena. … Finally, *methodological reductionism* is related to the scientific techniques used to decompose the hight-order [sic] entities into their low-order elements. **[These are not definitions**[12]**]** (2015, p. 263, their emphasis)

They aim at showing that with such an account, TOFT is reductionist.

We start with the so-called theoretical reductionism. While 'reducing terms' is nothing like 'reducing theories' (see references in the Appendix), it is still much better than what the critics do with it:

> Soto and Sonnenschein's works rigorously use the same vocabulary as the one used in classical molecular biology. TOFT talks about *cells, stroma, genes*. It does not consider new terms that we [sic] could not be reduced to words referring to elementary components. … Thus, as regards *theoretical reductionism*, TOFT cannot be said to be anti-reductionist. (2015, p. 263, their emphasis)

Happily, the critics count the words. With such a line of reasoning, "Julia eats her ice-cream" and "Her ice-cream eats Julia" mean the same thing, since they are composed of the same words. However, even indulging for ice cream, they are blatantly wrong. TOFT makes a central use of the (irreducible) notion of *tissue field*, as rightfully noted for instance by Bertolaso (2016, p. xi). The notion of 'constraint on the default state' has been introduced in a paper cited by the critics (Sonnenschein et al., 2014), and further elaborated (Longo et al., 2015; Soto et al, 2016). On a side note, in addition to considering new terms, TOFT also excludes several theoretical notions such as 'cancer cell', 'information', and 'growth factor' (Sonnenschein and Soto, 2011; Longo et al., 2012; Sonnenschein and Soto, 1999). The latter, for instance, is excluded in virtue of the theoretical choice of the default state. (The word is still used, of course, as many molecules, such as Fibroblast Growth Factor or Insulin-like Growth Factors have it in their common scientific name.)

The critics are not luckier with the so-called ontological reductionism:

> TOFT gives more importance to tissues, but the tissues are considered as an ensemble of cells, and the cancer remains a cellular disease. (2015, p. 263)

Unfortunately, first, tissues also include the extra-cellular matrix and many other parts. Second, TOFT emphasizes the *organization* of tissues. The reduction of the tissue to its cellular components is the critics' own assumption. Following them, organisms are ensembles of cells, and all diseases are actually cellular diseases, including auto-immune diseases and aneurysms. Pushing this line of reasoning one step further, all diseases are molecular diseases or even diseases of subatomic particles.

Now comes the methodological reductionism:

> The experimental protocols developed by the partisans of TOFT do consider cells and molecules, hence their methodologically reductionist stance. (2015, p. 263)

This is a far cry from what Marcum, from whom they borrow the concept, would endorse: "Researchers utilize this type of reductionism to investigate just the elements or parts and not the complex entity as a whole." (Marcum, 2009, p. 269). Methodologically speaking, TOFT does not consider 'just' the elements or parts. The hypothesis that there is no such thing as a cancer cell implies that one has to consider at least simplified tissues (in tissue culture) in order to be able to discuss the disease. In general, the ultimate proofs are *in vivo*, and the work of the Soto and Sonnenschein laboratory includes 2D culture, 3D culture, explants, transplants and *in vivo* work.

Soto, Sonnenschein and colleagues clearly state their method: they propose to start from the level at which the phenomenon is defined and to go up and down the scales (Soto et al, 2008, pp. 11, 13), as does Noble with his middle-out approach (Noble, 2006).

Thus, the critics, after having missed what it means for TOFT to define a tissular level, prefer to focus on inside/outside relationships defined at the cellular level:

> Thus, rather than considering a *cellular* and a *tissular scale*, we prefer to use the notions of *interior* and *exterior* of the cell. (2015, p. 264, their emphasis)

[12] To be fair, we refer the reader to Marcum (2009, p. 269) who, we think, is more precise.

They then claim that the definitions proposed by Marcum are inconsistent with the anti-reductionist claims in TOFT:

> This remark does not mean that TOFT is strictly reductionist, in all the possible meanings of this concept. It just shows that the assertion that *TOFT is an organicist theory* is not coherent with the conception of reductionism and organicism it is based on. This idea is not only applicable to Soto and Sonnenschein's work, since other authors, as Marcum (2010), consider TOFT as an organicist theory without coherent and strong arguments. (2015, p. 265, their emphasis)

Unfortunately, to substantiate this claim, the critics do not cite any paper on organicism but Marcum's. This is unfortunate because, as the critics' themselves note in their conclusion, the question of organicism was their very subject:

> [T]his claim for an integration of TOFT and SMT is not new (Marcum, 2010; Rosenfeld, 2013; Coffman, 2005). However, our original contribution [was to] … question the relevance of the reductionism/organicism opposition in the field of carcinogenesis. (2015, p. 266)

This failure to cite the literature relevant to the core of their argument comes, we think, from a biased reading of the TOFT/SMT literature.

3.5 The importance of pluralism

The critics compare their view to the integrative pluralism of Mitchell (2004). They only wave, however, at a plurality of causes (see also e.g. 2016, p. 85), they never flesh out a pluralism of models, not to speak of theories:

> Insofar as TOFT and SMT describe two compatible causal pathways, they can be integrated in a single approach to explain carcinogenesis. And this integration [of TOFT and SMT] is of a *higher epistemological value* than SMT or TOFT taken separately. (2015, p. 265, their emphasis)

The critics never show how "this integration" would be feasible, neither why it would be of higher epistemological value. It is however unclear which pluralism they defend:

> This view [the plurality of causes] is closed [sic] to the ideas exposed by Sandra D. Mitchell about biological complexity (Mitchell, 2002, 2004). (2015, p. 265)

Indeed, Mitchell (2004) has inflected her integrative pluralism to explicitly argue against causal closure[1] a la Kim in science, a causal closure that the critics vividly hold (see below). Eventually, their pluralism seems to boil down to the mere non-elimination of any theory:

> In other words, available scientific data suggest a *limitation of the domain of validity* of SMT, but they do not establish that the explanation of carcinogenesis provided by SMT is *never* valid. (2016, p. 82, their emphasis)

This is, however, a classical induction problem. To take a comparison, Lavoisier never proved that the phlogiston theory was never valid (actually, it did a great job at explaining the properties of metals, see Kuhn (1962, pp. 99, 148)). He just proposed another one.

3.6 The importance of (non-)physicalism

The main piece in the 2016 follow-up paper is a manifesto by the critics in favor of the causal closure of the physical world. Being charitable, they do not think that their targets may have a different view than theirs. Here again, however, they have missed a crucial paper:

> However, their response to our article enables us to identify a confusion often made by the proponent of TOFT **[Unfortunately, the critics do not give any reference]**: if they are opposed to a certain form of genetic reductionism, they are not opposed to reductionism in general.
>
> To be authentically anti-reductionist, they have to define a level of organization which would be ontologically different **[This is the tissue]** that [sic] the one used in the frame of SMT (that is to say, individual cells). To take a comparison, the advocate of an anti-reductionist view of carcinogenesis would have to explicitly consider that there is the same difference between *a tissue* and *an ensemble of cells* that [sic] between *the mental level* and *an ensemble of neurons*. Second, they would have to show that this new level of organization has a causal power on the cells, which cannot be reduced to the physical interactions between the cells and their environment. In other words, they have to defend the existence of an authentic *top-down causality* from the tissue to the cells **[They do: see Soto et al (2008)]**. Yet, this question of the top-down causality is tricky. Following (Kim 1988) [sic[2]], we think that the *closure of the physical world* is a fundamental principle which is hard to deny. (2016, p. 83, their emphasis)

Soto et al (2008, p. 5-7) have however argued that causal closure is founded on a principle itself 'based on a hidden logical fallacy':

> *… Kim jumps from the level of a finite system to the level of the world. How is it possible to make this jump? Obviously, this cannot be done on science alone! And the answer is historically well known: one needs a Demon. … [I]n order to become a physicalist – to reduce the real world itself to a set of physical events – the physicist needs a God's-Eye View (Putnam, 1990) … Yet, how can we accept the help of a supernatural entity on the one hand, if on the other we want to reduce the real world to a set of physical events?* (Soto et al, 2008, p. 6)

[1] That is to say "the idea that every event has a physical cause, assuming it has a cause at all" (Stoljar 2017).

[2] We cite him here as Kim (1998).

Whether one buys the argument or not, if one is to criticize TOFT authors' views on causality, this paper is a big piece missing in the discussion. The critics pursue:

> In particular, the advocates of TOFT do not bring strong arguments showing that the tissues exert an authentic top-down causality on the cells **[See again Soto et al (2008)]**. On the contrary, we argue that the advocates of TOFT, including Bizzarri and co-workers, defend a typical *physicalist reductionism*, despite their explicit criticism of both physicalism *and* reductionism: their article refers to biophysical forces **[The expression 'biophysical forces' does not exist in the paper[3]]** applied to the cells (which is a **[bio?]**physicalist way of thinking). (2016, p. 83, their emphasis)

Contrast this alleged 'physicalist way of thinking' with the original paper by Bizzarri and Cucina (who also happen to cite Soto et al, 2008):

> *Indeed, in the context of complex systems, physical forces and constraints acquire new properties (emergence) that are not anticipated or fixed at the beginning of a process: mechanical force may acquire novel properties, such as that of inducing gene expression, which cannot be predicted from our knowledge of the physical world.* (Bizzarri and Cucina, 2016, p. 225)

The critics go on:

> Besides, they [Bizzarri and Cucina] define reductionism as ''the concept for which every phenomenon can be explained by those universal principles governing the smallest components participating in the observed phenomenon'' **[Bizzarri and Cucina (2016) cite Nagel (1998), which the critics do not indicate]**. Yet, the notion of *molecular architecture* of the tissues is often used to expose and defend TOFT (Soto and Sonnenschein 2011) **[The expression 'molecular architecture' does not exist in the paper. That of 'tissue architecture' does]**, and it is hard to justify that DNA is ''smaller'' that [sic] the molecules of the extra-cellular matrix. We definitely agree that the general architecture of tissues **[This is not the same as that of the extra-cellular matrix]** can have an effect on cell proliferation. But this affirmation does not deny the principle of physical closure; in other words, it is logically possible to defend the role of tissues in promoting carcinogenesis in a reductionist frame **[In TOFT this is logically impossible since tissues are considered irreducible to their parts]**. We think the assimilation of TOFT to an anti-reductionist theory is based on a confusion between reductionism, as an ontological frame, and genetic determinism, as a causal mechanism **[It is difficult to see how this conclusion is warranted]**. (2016, p. 83, their emphasis)

In our conclusion we propose an interpretation of the approximations and misunderstandings exemplified in these passages.

[3] It exists in other papers of this literature. However, forces in this context have different theoretical roles than in classical mechanics: for example they are constraints on the default state (Soto et al, 2016; Montévil et al, 2016).

4. Conclusion

> Since new paradigms are born from old ones, they ordinarily incorporate much of the vocabulary and apparatus, both conceptual and manipulative, that the traditional paradigm had previously employed. But they seldom employ these borrowed elements in quite the traditional way. Within the new paradigm, old terms, concepts, and experiments fall into new relationships one with the other. The inevitable result is what we must call, though the term is not quite right, a misunderstanding between the two competing schools. … Only men who had together undergone or failed to undergo that transformation would be able to discover precisely what they agreed or disagreed about. Communication across the revolutionary divide is inevitably partial. (Kuhn, 1962, p. 149)

Errare humanum est, and we would not pretend to be immune to the same sort of mistakes that we have reviewed here. However, the wealth of errors, deformations and misinterpretations exemplified by the critics cannot be the product of chance alone: a biased view must have presided to the redaction of their papers. We suggest this is the SMT paradigm. Trapped in the old paradigm, the critics were not in a situation to understand TOFT. Having already crossed the divide (e.g. Vallat et al, 2013), we hope to have done better justice to their arguments. As such, the contribution of the critics is valuable from a historical point of view, as an illustration of Kuhn's thesis, written on a page – ironically – sandwiched in between two pages cited by the critics themselves (Bedessem and Ruphy, 2016, p. 84-85).

To us, a theory proposes a perspective on natural phenomena, a way to understand them. Changes of theory are changes of perspective, new ways to look at nature and to make sense of it. Science is a prolific activity and a field can host several incompatible theories entertaining rich relationships, as is the case in physics (Batterman, 2001). This means that reductive unification, as desirable as it may seem, is *de facto* a fiction. Rather than scaffolding on this fiction, we advocate an examination of the mathematical and conceptual flesh of theories. Such an examination should question whether theoretical thinking as we presently know it in physics is adequate for biology (Miquel, 2011; Montévil et al, 2016). In any case, we are confident that the challenges of XXIst century biology will require a great deal of genuine invention.

Appendix

We would like to advise the critics and other readers new to the debate to read the following literature in addition to the references cited above:

TOFT:

See the special issue in *Progress in Biophysics and Molecular Biology*: "From the century of the genome to the century of the organism: New theoretical approaches"[4] dedicated to the development of a theory of organism, a more general framework in which TOFT takes place and to which we contributed. (This was released in October 2016, but authors of the special issue would have happily shared preprints had the critics deemed desirable to contact them.) For the criticisms of the vocabulary of SMT see e.g. Sonnenschein and Soto (2011); Longo et al. (2012). While we would depart from some of her theses see also the book by Bertolaso (2016).

REDUCTION:

The whole field is missing from the critics' papers, although it is one of the most active areas in philos-ophy of science, and the very subject of their papers. As an entry, see the articles on the Stanford Ency-clopedia of Philosophy by van Riel and Van Gulick (2016) and Brigandt and Love (2015). For papers more directly connected to the debate see Malaterre (2007) (who tackles questions similar to the critics'), Bitbol (2012), Longo, Montévil and Pocheville (2012), Longo and Montévil (2014), and in particular Sarkar (1992) and Gilbert and Sarkar (2000). The book by Sarkar (1998) is an authority.

TOP-DOWN CAUSATION:

See Craver and Bechtel (2007) for the received view and Soto et al (2008) for the TOFT view.

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[4] These are Soto, Longo and Noble (2016); Soto, Longo, Montévil and Sonnenschein (2016); Soto, Longo, Miquel, Montevil, Mossio, Perret, Pocheville and Sonnenschein (2016); Sonnenschein and Soto (2016); Perret and Longo (2016); Mossio, Montévil and Longo (2016); Montévil, Speroni, Sonnenschein and Soto (2016); Montévil, Mossio, Pocheville and Longo (2016); Miquel and Hwang (2016); Longo and Soto (2016).

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