Cancer Modeling: the Advantages and Limitations of Multiple Perspectives

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Abstract
Cancer is a paradigmatic case of a complex causal process; causes of cancer operate at a variety of temporal and spatial scales, and the respects in which these causes act and interact are diverse. There are, for instance, temporal order effects, organizational effects, structural effects (due to size and shape, for instance, of a solid tumor), and dynamic relationships between causes operating at different temporal and spatial scales. Because of this complexity, models of cancer initiation and progression often involve deliberate choices to focus on one time scale, one causal pathway, or one aspect of cancer's dynamics. As in most of biology, modeling cancer involves simplification and idealization. At the same time, theoretical perspectives inform the construction of these models. Such perspectives might involve viewing cancer 'as' a genetic disease, metabolic disease, stem cell disease, an infectious disease, or a disease of tissue disorganization. This paper will argue that purportedly competing theoretical views of cancer are not at odds, but can (and should) be viewed as mutually informative. Models are most often developed in the service of asking very specific questions, and this requires limiting our view of the phenomena to a specific temporal or spatial scale, a particular cause, or a particular outcome, dynamic, or pattern. Thus, while some models may seem at odds, often they are simply concerned with different questions, or, they are complementary and mutually informative. I hope to bring this case to bear on debates among philosophers of science over perspectivism and realism, as well pluralism about the aims and scope of scientific theory.

> This dialectical tension, as it may be called, between a realist and an instrumentalist attitude, existing together without contradiction, seems to me characteristic of the deepest scientists. (Stein 1989, 64)

1. Introduction

In his *Structure of Scientific Revolutions*, Thomas Kuhn offered up a controversial account of scientific change. According to this picture, competing paradigms in the history of science are incommensurable. Scientific revolutions are revolutionary exactly because they involve a radical shift in worldview, or a "Gestalt" shift. Kuhn claimed that scientists operating under different paradigms quite literally "see" the world differently: "after Copernicus, astronomers lived in a different world" (Kuhn 2012, 117). This picture of scientific change has been enormously

influential—particularly in the context of the realism/anti-realism debate in philosophy of science. Kuhn is typically read as a "constructivist" and an "anti-realist."[1] For Kuhn resisted the view that the aim of science is "a permanent fixed scientific truth, of which each stage in the development of scientific knowledge is a better exemplar" (Kuhn 2012, 172-173). Instead, he compared scientific change to evolution by natural selection. Just as evolution is not directed at a fixed goal, so too our best scientific theories are at best good enough to survive the trials they face, at least relative to the going alternatives, at this particular time and place. Success in science is not a view from nowhere, but the best possible view from here.

On the one hand, many historically and naturalistically inclined philosophers of science have been sympathetic with Kuhn. Scientists are not in the business of gaining, as Giere puts it, a "view from nowhere or everywhere at once" (Giere 1999, 80), but with solving much more circumscribed problems or addressing very specific questions, in service of which they often generate models that are intended to represent the world in some respects, and to a greater or lesser degree of accuracy (Giere 1999). Fit of model to the world is a matter of meeting standards that are to some extent conventional and contingent upon historically available tools. The methodological standards, and, indeed, the conceptual frameworks of a given disciplinary specialty are to a large extent socially and historically "situated" (Massimi 2018, 345). Moreover, one often finds that, as Massimi explains, "Both across historical periods, and in any given historical period, science witnesses a plurality of models, theories, experimental techniques, and measurement apparatuses—all designed to investigate the very same target system" (Massimi 2018, 344). That is, even within a particular period, scientists may deploy a variety of different and, sometimes, apparently inconsistent models, all in service of investigating the same general phenomena.

How can scientists consistently deploy models making different and apparently incompatible assumptions? One answer to this question is to suggest that any incompatibilities will or should ultimately be jettisoned. Another answer is that we ought to view models at best as tools for prediction. The former view is favored by realists; the latter view might be favored by anti-realists or instrumentalists. The debate has now raged for decades. Is there a middle ground

[1] Or at least this is one very influential reading of Kuhn, though one Kuhn protested (1977).

in this debate?[2] Giere (1999) proposed a view he called "perspectival realism" as a sort of middle ground between extremes on this continuum:[3]

> Rather than thinking of the world as packaged in sets of objects sharing definite properties, think of it as indefinitely complex, exhibiting many qualities that at least appear to vary continuously. One might then construct maps that depict this world from various perspectives…. Here we have a way of combining what is valuable in both constructivism and realism…. We can agree that scientific representations are socially constructed, but then we must also agree that some socially constructed representations can be discovered to provide a good picture of aspects of the world... (Giere 1999, 26)

Giere's proposal has two parts: one metaphysical and another epistemic. The metaphysical thesis is that the world itself is "complex"; or, objects are not fixed and easily demarcated, and their properties often vary continuously.[4] The epistemic claim is that, given the complexity of the world as we find it, our scientific representations of the world are (inevitably) partial, or in some sense "perspectival." Giere's appeal to map-making is central to his argument; scientists build models on the same sorts of principles that mapmakers build maps. Like maps, models represent the world only partially, or represent the world only in some aspect, and with some degree of accuracy. Indeed, some aspects of models may be deliberately fictional or involve misrepresentations. Just as maps require interpretation, scientific models must be interpreted in part by appeal to the intentions or interests of the modeler. One needs to know which aspects of the model are intended to represent which parts of the world in order to determine if a model is a good one. Giere thus sums up two main features of perspectivism: "First, there is no total or universal perspective, or, alternatively, there is no perspective from nowhere or from everywhere

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[2] There are, as a matter of fact, several "middle ground" perspectives that have been offered, some to the effect that the debate proposes a false dichotomy. See, e.g., (Stein 1989; Fine 1984).

[3] Giere's proposal was initially intended as a middle ground between extreme versions of "objectivist" scientific realism (the thesis that theories can in principle provide "a complete and literally correct picture of the world itself " [Giere 2006b, 6]) and constructivist antirealism ("scientific claims about any reality beyond that of ordinary experience are merely social conventions" [Giere 2006a, 26]).

[4] There are, of course, a variety of competing views about what it means to say that the world is in some sense "complex." For a discussion, see, e.g., (Simon 1962), (Wimsatt 1994), and (Mitchell 2003). Perhaps it is needless to say that not all agree that the world (in general) is complex or in what sense(s). My own view is that perhaps only some types of systems exhibit both what Simon (1962) calls "organizational" and "dynamic" complexity: e.g., organisms, beehives, cities.

at once. All perspectives are partial relative to their objects. Second, there is something real that each perspective is a perspective of" (Giere 1999, 80). Giere's perspectivism is thus "realist" in the sense that our scientific perspectives are of the world: we can and should interpret models as representing the world more or less accurately. Yet, like Kuhn, Giere grants that what and how scientists come to know is shaped in part by scientists' historical context and particular interests.

Recently, several philosophers of science have either critiqued or refined Giere's perspectival realism (Chakravartty 2010; Morrison 2011; Chiramutta 2016; Massimi 2018). All these authors wish to defend a form of realism; however, they disagree about what to make of the fact that scientists often deploy diverse, sometimes apparently incompatible models of the same systems. For instance, some argue that seemingly incompatible models are, as a matter of fact, not incompatible, because each describe the actual dispositions of a real-world target, but differentially revealed by different methods of detection (Chakravartty 2010). Others contend that, while in some cases inconsistent models are simply incompatible, in that they ascribe inconsistent "fundamental properties" to the target of inquiry (Morrison 2011, 351), in other cases, apparently inconsistent models are simply different ways of elaborating the same set of basic principles. A unified treatment, based on shared basic principles, is possible, once the falsely attributed properties are jettisoned. Others still argue that the relationships between models and the world are "haptic" rather than "perspectival," interactive, interested, and historically situated (Chirimuuta 2016). Similarly, some claim that across perspectives, successful claims of scientific knowledge from one perspective may also meet standards of adequacy when assessed from other perspectives (Massimi 2018).

In my view, each of these authors provides insight into scientific models and modeling. The key to reconciling them is to recognize that modelers use models for different purposes. Sometimes unity and assimilation is the goal, for the reasons Chakravartty and Morrison suggest; however, sometimes, apparent disunity and inconsistency are not only tolerated but also, indeed, maintained (apparently) indefinitely. In part, this may be because scientists often do not know which of the two is the likely outcome ahead of time! As Stein has argued, the very best scientists straddle the "dialectical tension" between realism and instrumentalism. By way of example, Stein points to Maxwell's treatment of the ether:

> If something is transmitted from one particle to another at a distance, what is its condition after it has left the one particle and before it has reached the other?.... In fact, whenever energy is transmitted from one body to another in time, there must be a medium or substance in which the energy exists after it leaves one body and before it reaches the other, for energy, as Torricelli remarked, 'is a quintessence of so subtle a nature that it cannot be contained in any vessel except the Inmost substance of material things'. Hence all these theories lead to the conception of a medium in which the propagation takes place…. If we admit this medium as an hypothesis, I think it ought to occupy a prominent place in our investigations, and that we ought to endeavour to construct a mental representation of all the details of its action, and this has been my constant aim in this treatise. (Maxwell 1881, 438)

Like Maxwell, many scientists seem to be capable of holding in mind simultaneously both realist and instrumentalist stances, holding both that a theoretical posit is real "enough" to exhibit regularities that can be investigated, but granting at the same time that their role in one's theory or model may at best be instrumentally useful in inspiring further inquiry. Or so I will argue, below.

It's also true, of course, that scientific models are constructed in service of performing different functions. All models are in some sense a representation of the world, but representations may be intentionally sketchy, contain deliberate misrepresentations of some part or feature of a system, or be intended (for now) as simply predictive tools. If we grant this, the realist and antirealist need not part ways. Moreover, while some models are general, many treat only a subclass of cases of phenomena that meet specific (restricted) conditions. In such cases, there is no direct contradiction between models; a unified picture that incorporates all such models is not the ultimate aim. Fagan (2017) has recently drawn upon the literature on modeling and perspectival realism to generate a taxonomy of different sorts of relations that might obtain between models:

- direct conflict
- simple additivity
- subsumption
- interactive process

- cross-perspective translation
- no cumulative interaction
- non-interaction
- complementarity

She explains and describes these relations as follows:

> Direct conflict is the objectivist view, such that we select the best model among alternatives. Simple additivity is the bare conjunction of statements from different models associated with different methods. Subsumption by more basic principles (traditional unification) is an indirect relation between models—each is subsumed by the shared basic principles. The idea of an interactive process is not a relation per se, but part of a more general framework for thinking about these relations (see below). Cross-perspective translation is a kind of interactive process, but with distinctive features…. Noninteraction is a limit case: absence of a relation between models in practice…
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> …simple additivity involves no substantive connection between models from different perspectives; their contributions are simply strung together in a conjunction. The "unification" of simple additivity is bare logical consistency…
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> …complementarity is a familiar relation…models from different perspectives can complement one another through differences that do not converge on a common core…models in different perspectives are, at some point in their construction, fitted together like jigsaw puzzle pieces. I therefore term this category of relation "complementary." Cross-checking and mutual constraint on possibility space are examples. (Fagan 2017, 27-28)

This taxonomy will be useful in our consideration of the varieties of model-relation in the context of cancer research. In my view, there is a patchwork of kinds of relation between models in cancer research. Sometimes, apparently competing or inconsistent models of cancer initiation or progression are simply concerned with different questions, or different targets, at different scales of analysis. Ultimately, however, I will argue that complementarity, not conflict, is the

proper view of the relationship between purportedly competing perspectives on carcinogenesis that I consider in some detail below.

First, however, it's important to note briefly that there are many kinds of thing referred to as "models" in cancer science, some "concrete," and some more "abstract." For instance, model organisms, or cancer cells in culture are often treated as "models" or experimental systems for investigating various features or aspects of cancer. In contrast, more abstract models include mathematical representations of cancer's dynamics using ordinary differential equations, agent-based computer simulations of changes in cancer cells over time, network models of signaling pathways, or "box and arrow" diagrams of core causal pathways in the cell associated with tumorigenesis. The aims of these more abstract models are diverse. Sometimes they serve as a starting point for developing and testing causal hypotheses; sometimes they are used to make very specific predictions, suggest avenues for intervention, or are used simply for pedagogical purposes. Scientists may wish to investigate the conditions on or features of a kind of dynamic process; such investigations are more theoretical in character. However, much of modeling in cancer research is concerned with practical matters, such as predicting the course of a cancer type or subtype, or estimating the age of onset, likely response to chemotherapy, or threat to mortality of different cancers. Some of the models are very general; some are highly specific. Given the variety of functions they are intended to serve, and the variety of things scientists characterize as "models," it would be difficult at best, and foolish at worst, to attempt to offer a general account of the relations between and functions of models in cancer science.

Nonetheless, Giere's picture of the relationship between "theories" and "models" is helpful as a first pass, when considering the construction and roles of formal models of cancer. Formal models of cancer's dynamics or progression are in large part informed by or built on the principles of "theories" (or, as I prefer, research traditions),[5] though such principles are often consistent with a variety of different modeling strategies. For instance, some mathematical models built on the principle that cancer is a multi-stage process driven largely by acquisition of

[5] I take it that some families of models are informed by a research tradition that includes a commitment to certain claims as well supported by evidence, but nothing like a set of laws or "theoretical" principles. It's unhelpful to speak of "theories" in this context, at least in the sense of law-like exceptionless generalizations about cancer initiation or progression of the sort that philosophers (at least historically) have identified with laws of nature. Instead, going back as far as Virchow's (1863) proposal that cancer may result from irritation, it's rarely (if ever) the case that cancer scientists assume or confidently assert (unless they're being incautious or writing for a popular audience) that any particular distal cause or proximate mechanism is a necessary condition on cancer. Instead, over the course of the history of cancer research, viruses, "oncogenes," "tumor suppressor" genes, metabolic changes to cells, or "stemness" properties, are taken to be highly probable, plausible, or likely candidate causes of cancer initiation, progression, or recurrence.

mutations represent cancer initiation and progression as akin to a dynamic, evolving population; others take populations of cells in a tumor as engaged in a process of "competition" akin to competitive exclusion modeling in ecology. Models built on the principle that cancer is shaped by epigenetic factors that affect developmental pathways may represent cancer as a shift from one stable or equilibrium state of organization or developmental homeostasis to another, where stable states are equilibria points on an epigenetic landscape. Other formal models built on the same principle might represent the relationship between gene products and signaling molecules in the tissue microenvironment as vast signaling networks, reorganized by cancer. These modeling strategies are affiliated (very roughly) with some overlapping commitments or theories of carcinogenesis, broadly understood. None, however, relies exclusively on one "theory" to the exclusion of others. Rather, each draws upon various presuppositions about what sorts of causes are significant in cancer initiation and progression: mutation, epigenetics, or, organization or dynamics of developmental pathways. That said, all such models more or less accept some fundamental assumptions: that cancer cells are phenotypically different from normal cells, in part due to their genetic or epigenetic changes, and in part due to many other factors at work in the tissue microenvironment. Indeed, we can (and in many cases have) identified the "driver" mutations and epigenetic factors responsible for these particular phenotypes.

The so-called "oncogene" paradigm, according to which mutations to specific genes play essential roles in the generation of a cancer phenotype at the cellular level, has dominated at least the last thirty years of cancer research. More peripheral research programs have focused attention on the role of the tissue microenvironment (Sonnenschein and Soto 1999), cellular metabolism (Warburg 1926; Seyfried and Shelton 2010), the role of structural or developmental organizing factors (Bissell et. al. 1999), or stem cells (Clarke et. al. 2006) in cancer initiation and progression. This focus on different kinds of causes or causal pathways may prima facie appear inconsistent. It's my view, however, that these are not incommensurable. Instead, they are research programs focused on simply different causal pathways, all of which are indeed relevant to cancer, and they can be integrated into a more comprehensive view of cancer's origins. Models of carcinogenesis that focus on one particular, local causal pathway are not fundamentally in tension with models of broader networks of pathways. For, as a matter of fact, cancer is a complex, dynamic process, requiring attention to multiple temporal and spatial scales,

from short-term molecular interactions, to mid-term developmental processes shaping tissue organization, to the history of life on earth and the emergence of multicellularity.

To situate my view, then, viz. the views discussed above, then, I do not take theoretical unification as the exclusive goal of scientific inquiry. Sometimes perspectival models are complementary; other times, they are simply taken to be competitors for heuristic or exploratory purposes (Massimi, forthcoming). Indeed, the hope for a unified theory of cancer, if by this one understands a set of necessary and sufficient causal conditions on all cancers, or universal laws of carcinogenesis, is simply misguided. Rather, there are many useful perspectives on cancer, or research programs that focus on one type of cause or on one temporal or spatial scale. Models that may appear inconsistent can be reconciled once one situates them in a larger context or interprets them appropriately. There are two components of my argument for this claim: one historical and one philosophical. These will correspond, roughly, with two parts of the paper.

First the historical: In her recent book, *Cancer Stem Cells: Philosophy and Theory*, Laplane argues that cancer stem cell theory is a "revolutionary" new theory of cancer initiation and progression that offers to "break the stalemate in the war on cancer" (Laplane 2016, 2). She contrasts cancer stem cell (CSC) theory with what she calls the "classical conception" of cancer initiation and progression. She claims that the classical approach cannot explain, and did not predict many important features of cancer. In particular, the classical view cannot explain and did not predict the genetic and phenotypic heterogeneity of cancer cells in a tumor, and the causes of resilience to chemotherapy. This book echoes similar books claiming "revolutionary" approaches to cancer. In 1999, Soto and Sonnenschein argued in *The Society of Cells: Cancer and Control of Cell Proliferation* for a "new paradigm" of cancer research: the "tissue organization field theory" (TOFT), which they contrast with the somatic mutation theory (SMT). Sonnenschein and Soto contest what they take to be the universally held "dogma" that somatic mutation is the cause of cellular proliferation. In their view, cancer results from a breakdown of tissue organization that disrupts the normal inhibitions of proliferation that are inherent in the tissue architecture of a multicellular society of cells. In each of these cases, a new paradigm is contrasted with the old, and promises are made on behalf of the new for both understanding and treatment of cancer. Are these alternatives genuine "paradigm" shifts, involving incommensurable views about the causes of cancer? Is the choice between purportedly competing views so stark? Some (Malaterre 2007; Bertolaso 2011) have argued that this is a

mistaken way of thinking about the SMT v. TOFT debate. In this paper, I make a similar argument, viz. a more recent debate in the history of cancer research concerning cancer stem cells. Like Malaterre and Bertolaso argue in the context of SMT v. TOFT, I argue that this debate is better characterized as a gradual shift in understanding and assimilation of novel ideas. The stem cell theory and "classical" approach are not so starkly at odds, representing incompatible theories. Indeed, in my view, progress in cancer research is not well framed as shifts in theory; cancer research is largely problem-driven, as opposed to theory-driven. There are few if any paradigm shifts in science, and cancer science is no different in this respect from other cases. This is piecemeal theory change rather than replacement, and perspectival realism can shed light on how. The contrasts offered up between these different perspectives on cancer are not between incommensurable worldviews. This is my historical thesis.

Second, my philosophical thesis is intended to dovetail with the historical thesis. Searching for a unified theory or one necessary condition on carcinogenesis is exactly the wrong strategy. Contrary to defenders of these "revolutionary" new theories, cancer is not either a disease of mutations *or* a disease of the tissue microenvironment, a disease of genes *or* a disease of stem cells. Rather, each of these research programs provides a novel but *partial perspective* on a complex, heterogeneous disease. Each approach has shed light on the mechanisms that yield cancer, though emphasizing quite different temporal and spatial scales.

The view I defend here, in other words, may be characterized as a kind of theoretical pluralism. According to Beatty, this is the view that a domain of inquiry is "essentially heterogeneous, in the sense that a plurality of theories or mechanisms is required to account for it…. There is no single theory or mechanism—not even a single, synthetic, multi-causal theory or mechanism—that will account for every item in the domain" (Beatty 1995, 65). Beatty has suggested that we ought to expect theoretical pluralism in the biological sciences. His rationale is as follows:

> …why should we adhere to a methodology that dictates the search for unity accounts of each domain of biological phenomena—e.g., a unitary account of inheritance, or a unitary account of carbohydrate metabolism, or a unitary account of gene regulation, or a unitary account of speciation—unless we have reason to believe that the outcomes of evolution are highly constrained?

> …unless we believe the outcomes of evolution are always severely constrained, then perhaps we should be on the lookout for mutliple accounts in each domain. (Beatty 1995, 75)

Beatty thinks that unless we have special reason to think that a biological process is evolutionarily constrained, we ought to seek out not unitary but pluralistic accounts of phenomena. Is the pathway to cancer constrained either from an evolutionary perspective or otherwise? In some sense the pathway is constrained, but this is only insofar as all cells in a multicellular organism are the product of a long history of evolution of cooperative organization. However, constraints on disruptive growth have evolved in different ways in different tissues (and, indeed, in different sexes and different species!); many different constraints on cancer have been selected for and there are also many ways in which these constraints fail. This is why cancer is, after all, not one disease; each cancer has its own distinctive site of origin and so also its own distinctive pattern of failure, unique genetic signature, pattern of progression, and likely outcomes, as well, of course, as distinct remote and proximate causes, from viral infection to environmental factors. Cancers are heterogeneous in a variety of senses, both genetic and phenotypic, or, if you like, distinct in ontogeny and phylogeny. At only the most coarse-grained level of description is there one way in which a cell becomes a cancer cell, a cancer cell becomes a population of cancer cells, and a population of cells invades and metastasizes to neighboring tissues.

The right lesson to take away from the history of cancer research, in other words, is that the question of which among many possible research program is the most "unified" or "true theory" is simply the wrong question to ask. Giere's perspectival realism is useful here: in the face of complexity, making progress in science is not a matter of searching for one true theory or view from nowhere. The right way to consider the problem is to note how and why different research traditions are epistemically fruitful—where this means that it yields knowledge of causes or properties of the system that help us better understand, predict, and successfully intervene.[6] Now I will turn to my historical analysis.

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[6] Morange (2015) makes a similar (but more general) point. He argues that "in some cases…contrasts (between competing perspectives) are hardened by participants. Both sides demand that a choice be made between the different explanations. In other cases, the need for a choice vanishes when knowledge of the system under study increases…the

2. SMT v. TOFT

In 1999, Soto and Sonnenschein published *The Society of Cells*, in which they set out what they take to be incommensurable views of carcinogenesis. On what they take to be the widely accepted and yet false view—the somatic mutation theory (SMT)—mutations are acquired during somatic cell division by the precursors of cancer cells. Some such mutations yield the hallmarks of cancer—cancer cells proliferate, are not sensitive to apoptotic signaling (signals that indicate cells should become senescent), acquire a blood supply, and acquire the capacity to invade and metastasize. This picture of cancer, they argue, presupposes that the default state of metazoan cells is quiescence—cancer is a departure from this default, and the explanation for the departure from this state is, in their view, "reductionist." In contrast, they advance what they take to be a holist view, the "tissue organizational field theory" (TOFT). According to TOFT the default state of cells is proliferation, and the cause of cancer is disruption of reciprocal interactions between cells that ordinarily serve to maintain tissue organization. They argue that their picture of cancer can explain phenomena that SMT cannot; in particular, it explains and predicts the fact that cancers exhibit a great deal of heterogeneity, and that it's possible, by altering the tissue microenvironment, for cancer cells to revert to healthy, normal cells, and develop into differentiated tissue. Therefore, in their words, we ought to adopt this novel paradigm, and reject the false and failed alternative.

There are two components of my argument; one historical and another conceptual. First, it's not clear to me that any advocates of the somatic mutation theory (whom Soto and Sonnenschein only rarely identify) ever were committed to the view they describe about the default state of cells, or, for that matter, that a single or few oncogene(s) may induce cancer. In other words, it seems to me that Soto and Sonnenschein give at best a very thin caricature of mainstream cancer researcher's views. Second, (perhaps not surprisingly) once we get a more robust picture of the mainstream view, we need not take these views as incompatible. Indeed, many of the classic studies that Soto and Sonnenschein cite in support of their novel theory are not only consistent with the presence of mutations in cancer cells but mutually reinforcing. There

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discontinuity (between approaches) is progressively disappearing" (Morange 2015, 40-41). The latter is very much the case in cancer research, in my view.

are reciprocal interactions between tissue organization and signaling pathways controlled in part by many mutations to cancer cells. By couching the issue as revolutionary, and so enforcing a sharp divide between precursors and successor paradigms, one is bound to view history as a vanquishing rather than a progressive adding on of novel perspectives on the same phenomena.

3. CSC Theory: Cancer Stem Cell Theory

In her recent book, the philosopher Laplane argues that the CSC theory (cancer stem cell theory) has various advantages over the alternative classical theory (Laplane 2016). Tellingly, she does not attribute the classical theory to any particular author or set of authors. In fact, she defines the classical theory primarily in terms of how it differs from CSC theory. So it may be helpful first to describe what she takes to be the four fundamental theses of CSC theory:

1. CSCs are capable of self-renewal, thus producing new CSCs.
2. CSCs are capable of differentiation, thus producing cells of different phenotypes.
3. CSCs represent a tiny subpopulation of cells, distinct from other cancer cell populations and are, in theory, isolatable.
4. CSCs initiate cancers.

It's worth noting that the first two claims, as she points out, concern the concept of a stem cell. The latter two claims concern carcinogenesis itself: how cancer arises. It's the latter two theses that Laplane takes to be in tension with the classical view. On the classical theory, she claims that "all cells are capable of self-renewal" (Laplane 2016, 33) and "different cell types are able to initiate new tumors" (Laplane 2016, 33). The capacity to initiate new tumors arises as a consequence of the acquisition of random mutations, what she calls the "stochastic model." This same capacity—the acquisition of random mutations and the evolution of cell lineages—also is taken to explain the heterogeneity of cell populations and the capacity for cells to acquire resistance to chemotherapy. She takes these additional commitments of the classical theory to be ad hoc, and contrasts this failure in "parsimony" of the classical view with her preferred CSC theory.

That is, she claims that CSC theory "explains cancer development, propagation and relapse" from a "limited number of hypotheses" (Laplane 2016, 28). In contrast, the classical view neither predicts nor explains these phenomena, but must invoke special ("additional" or "ad hoc" theories) to explain them. The CSC is thus more parsimonious than classical theory because it unifies a number of explanations, or shows how different phenomena can be explained by a common unified theory. In particular, the low clonicity of cancer cells and high heterogeneity of tumors is best explained by CSC. In contrast, the classical theory must invoke many different additional hypotheses. Thus, the CSC theory is more parsimonious than the alternative classical theory. Moreover, the CSC theory has the advantage that it "connects basic research and intervention by suggesting new therapeutic strategy" (Laplane 2016, 28)

It's not the case that these two theories are as a matter of fact inconsistent, once we begin to explore a point that Laplane herself draws our attention to: namely, that the concept of cancer stem cell is multiply ambiguous. Indeed, they are different variants on the same general theory, which disagree on one specific point: namely, the origins of cancer stem cells. To explain: if, as a matter of fact, all cells at least potentially may acquire the properties typical of cancer stem cells (which is an independent empirical question, evidence for which is still being gathered), then the CSC theory is perfectly consistent with the classical theory. Indeed, some populations of cells in a tumor appear to all have the features of a cancer stem cell or the potential to behave like a stem cell. That is, "stemness" is a property associated with certain capacities that are not fixed but acquired. The plasticity of many types of cancer cells makes it the case that many cancer cells can shift back and forth between "stemness" phenotype and non-stem phenotype. Given this, it appears that the CSC is just one of a continuum of general views, some of which take only specific types of cells to be precursors to cancer and others which grant that many different types of cells have the potential to develop such properties. But this points to a more substantial issue, one she herself is at pains to defend: stemness itself is a relatively unstable category in the cancer literature. Is stemness just a proxy for whatever properties there are that allow a cancer to arise? Is having such properties just what it *means* to be a CSC? For if a CSC is just any cell that initiates a tumor, then CSCs *must* exist (something must be initiating a tumor!) and the classical theory *must* endorse the existence of CSCs. It is by definition true that cancer stem cells exist if cancer stem cells are just those cells that initiate tumors. So the real question at issue here is whether the cells that initiate a tumor are in some way distinctive or require distinctive

precursors. But classical theories of carcinogenesis of course granted that the cells that initiate a tumor must possess a variety of features that make them distinctive. The real question is what features those are, which (at least initially) was an open question on the classical theory. So it's unclear then what the purported disagreement is about.

Moreover, the CSC theory is not as parsimonious as she makes out initially in chapter two. As Laplane later acknowledges in chapter five, the CSC theory can (and indeed must) help itself to the somatic evolution theory if it is to explain a variety of features of cancer development and metastasis. So this extra, or additional, hypothesis that renders the classical theory less parsimonious is one that the defender of the CSC theory (eventually) endorses as well.

The real innovation of cancer stem cell theory, in my view, is in giving a label to something that classical theory already acknowledged as a legitimate and even likely possibility. Namely, there are special or unique features belonging to all and only those cells that initiate a tumor and/or cells that propagate tumors or yield metastases. It is, after all, still an open empirical question whether any cell in the body is capable of acquiring these properties or only some. In other words, what is at issue between the two is whether all cells have the potential to acquire the properties of those cells that can initiate and propagate cancers. But this is a matter of debate within the CSC literature. So it's perfectly possible for defenders of the classical view to endorse (at least one version) of the CSC. The two are not so starkly opposed as Laplane makes out. As Laplane documents at some length, the very concept of a cancer stem cell is multiply ambiguous, in the following ways:

- First, when we speak of cancer stem cells, we may be referring to their capacities or properties, or to their historical role or genealogy, i.e., to the fact that they were the cells from which other cancer cells originate. That is, some take cancer stem cells to be defined in terms of their distinctive capacities and some in terms of their relationship to other cells—in particular, to their ancestor-descendent relationships in a population of cells in a tumor. The "cancer stem cell model" is sometimes simply taken to refer to any model of a tumor that treats the population of cells as having a hierarchical relationship, where one or a few cells propagate the tumor, whether or not those cells have distinctive properties that cause them to stand in that relationship.

- Second, there are several different kinds of historical role that CSCs might play: They may be all and only those cells that initiate a cancer under natural conditions, they may be those cells which propagate a cancer in situ, or they may be those cells that are capable of propagating a cancer in an experimental animal.
- Third, some take the concept of CSC to be restricted to normal stem cells, which some believe are the most likely precursors to cancer. Others hold that cells that originate a tumor have stem-like properties but may or may not derive from normal stem cells.

Cancer researchers have attempted to give greater clarity to the debates about cancer stem cells by using different terminology to distinguish between these different senses: "cancer-initiating cells," "cancer-propagating cells," "cancer stem-like cells," and so on. But in Laplane's view none of these attempts at clarification did the work the authors hoped. For it turns out that even the expression "cancer initiating cells" could refer to either precancerous cells that have acquired some but not all of the properties necessary to initiate a tumor, cancerous cells that initiate tumors in patients, or cancerous cells that initiate tumors in experimental animals. All three senses have been used in the literature, leading to some confusion.

Here's where it becomes clear that Laplane has set up a false dichotomy. She points out that different experimental conditions can lead to different results in the propagation of cancers in experimental animals. Under some conditions much higher percentages of cells in a tumor are capable of propagating a cancer in experimental animals. Whereas the initial experiments in propagation yielded a very small success rate—only .00001 percent of cells in leukemia or as many as 25 percent of cancer cells from a melanoma could propagate themselves in NSG mice, mice where a gene associated with the precursors to Natural Killer cells was disabled. Indeed, using different mice strains, and even different sexes of mice, yields greater or less success at propagation by a much higher percentage of "CSC" cells. Instead of viewing this as evidence in favor of the classical theory—namely, that any number of cells is capable of acquiring the features necessary to propagate a tumor—she suggests only that this evidence undermines "the idea that CSCs only represent a small fraction of cancer cells" (Laplane 2016, 94). But if CSCs are just any cell capable of propagation, this is by definition true. The real question at issue is whether any cell can acquire this capacity in the right circumstances or whether only some can. And this question is not definitively decided by such experiments, though they do lend greater

credibility to the classical model than Laplane acknowledges. In other words, it sometimes seems that Laplane, despite the fact that she acknowledges that the very expression "CSC" is multiply ambiguous, fails to recognize that it's this very ambiguity that leaves the door open to seeing the CSC and classical theory as overlapping and fully consistent perspectives.

4. Conclusions

How may this account of the recent history of cancer research be brought to bear on the debate over perspectival realism? Recall the taxonomy of relationships between models discussed by Fagan (2017):

- direct conflict
- simple additivity
- subsumption
- interactive process
- cross-perspective translation
- no cumulative interaction
- non-interaction
- complementarity

How can this picture help us make sense of debates among advocates of purportedly competing theories about cancer? We can see these alternatives as several ways in which competing "perspectives" can be reconciled. Of course, different authors mean different things by "perspectives." For Giere a perspective is akin to Kuhn's disciplinary matrix; for Massimi it is the scientific practice of a given community; for Teller (2001) it is a family of idealized and imprecise models. In this context I take a perspective to be a family of commitments regarding what causes are central or important to cancer, associated with a heuristic or framework, which helps us develop research questions, frame appropriate answers, and guide inquiry into cancer. All of these together make up a perspective. Different research programs have focused attention on different temporal and spatial scales or concerned themselves with one or another causal pathway as central to cancer initiation and progression. These in turn provide us with principles to build models of cancer initiation and progression. The "oncogene" paradigm identified a

variety of genes, mutation of which led to uncontrolled growth, failure of apoptosis, angiogenesis, and, eventually, invasion and metastasis. Early models of cancer growing out of this research tradition represent cancer progression as a step-wise, rate-limited acquisition of a series of mutations, eventually leading to uncontrolled growth.

Models growing out of "competing" perspectives or research traditions focused on the roles of tissue microenvironment and tissue architecture in cancer, the typical features and behaviors of stem cells in cancer, or the developmental pathways disrupted by or co-opted in cancer progression. For instance, one model which draws upon the cancer stem cell theory takes it to be the case that the differential incidence of cancers of different tissue types is largely due to the number and rate of division of somatic stem cells in different tissue types, given the relatively strong correlation between the two (Tomasetti and Vogelstein 2015). But this model is not in tension with the classical model. In fact, both models treat cancer as a step-wise, iterated, and rate-limited process, where mutations and epigenetic alterations eventuate in disease.

In some cases, these different models of cancer are concerned with different outcomes or classes of outcome at different scales. They focus on different causal pathways to cancer or are concerned with different scales of analysis (from the molecular on up to evolutionary history). So, on the one hand, we might say that these models are complementary and non-interactive; they are not in conflict, insofar as they are concerned with different questions. However, in other cases, several models have been developed for describing progression to disease, the dynamics of progression, or subsequent metastasis within a single cancer type or subtype, such as breast cancer. In these cases, there appears to be a relatively seamless integration of theory and data with mutual constraint, drawing upon evolutionary and developmental perspectives, knowledge about metabolic changes to cancer cells, and structural and developmental factors in cancer, genetics, and stem cell theory. Indeed, arguably, the classic multistage model predicts that the hierarchical structure of differentiation in tissue is a protective mechanism against cancer and thus serves as a kind of anticipation of stem cell theory. For if a normal self-renewing population of stem cells acquires mutations or epigenetic changes that yield increases in proliferation or resistance to apoptosis, then they can yield a cancer via somatic evolution (Pepper et. al. 2007). According to the current stem cell theory stemness properties could either be a defining feature of some subpopulations of cells in a tumor or could be a transitory property of all cells in a tumor. For cancer cells appear to be highly plastic and can transition back and forth between

stem and non-stem states (Kreso and Dick 2014). Ultimately, however, genetic changes, epigenetics, and changes to the tumor microenvironment all contribute to the emergence of disease. These perspectives are not in tension but complementary; and seeing how and why they are mutually informative has been a progressive, gradual process. The integration of theory and data is iterative, as more information about the various properties that contribute to cancer progression, heterogeneity, and resistance to chemotherapy, and their mechanistic bases, is acquired (Plutynski 2013). Massimi's interactionist approach seems the best fit here. Different models of the same cancer or cancer subtype (e.g., breast cancer) that focus on different causal pathways each relevant to the larger outcome can be seen as yielding complementary information about constraints on this process.

The attempt to tell this story as one of vanquishing the old and replacing with the new is, in my view, a mistake. This model of successive theory vanquishing, or of the replacement of one incommensurable paradigm with another, is inappropriate here and leads to unproductive battles. Instead, what has occurred is a progressive integration of diverse perspectives on the same phenomena or alternatively, in some contexts, the development of models concerned with slightly different, and equally important, questions or problems, or different targets of inquiry.

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