How is Cancer Complex?

Abstract

Cancer is typically spoken of as a “complex” disease. But, in what sense are cancers “complex”? Is there one sense, or several? What implications does this complexity have – both for how we study, and how we intervene upon cancers? The aim of this paper is first, to clarify the variety of senses in which cancer is spoken of as "complex" in the scientific literature, and second, to discover what explanatory and predictive roles such features play.

1. Introduction

There are two central aims of this paper. The first aim is purely descriptive. I provide a taxonomy of different ways in which cancer is *described as “complex*” in the cancer literature (see Table 1).[[1]](#footnote-1) A central upshot of this taxonomy is that cancer researchers are not consistent in characterizing what makes cancer “complex.” Very different features of cancer are taken as evidence for, or illustrative of, cancer’s “complexity”. (Of course, scientists will sometimes refer to cancers as “complex” in the merely *subjective* sense that cancers are difficult to investigate and understand. The concern of this paper is not with the ways in which cancer scientists find cancer difficult to understand, but with *why* they do: the *objective features* of cancer that warrant the label.)

The second aim is to explore whether these features do any explanatory work, and in particular, whether some such features tend to promote others. In some cases, there is evidence of a causal relationship between such features, suggesting that cancers serve as an instance of the kind of generalizations that complex systems are said to be governed by,[[2]](#footnote-2) though assessing this is complicated by two problems. First, many of the features identified as distinctive of complex systems (e.g., “self-organization,” “non-linear behavior,” “robustness,” “adaptation”) are either vaguely or inconsistently operationalized; so, whether cancer in particular is an instance of these general features may well depend upon which of several ways we are characterizing them. Second, even in the best cases, the evidence for such relationships in cancer is indirect. While we can find patterns of correlation between, e.g., “diversity of parts and interactions” and “robustness to insult,” in some cancers, it is rather difficult to generalize about whether and how these relationships hold as a general rule, given that, apart from the fact that many cancers are discovered relatively late, intervening experimentally on such system wide features *in situ* is prohibitively difficult. Often, the best we have is indirect evidence for how such properties can be intervened upon in model systems, computer simulations, or cell culture. In sum, it is difficult to judge the empirical warrant for generalizations about complex systems (such as that “heterogeneity” promotes “resilience” in cancer), not only because inconsistently operationalized, but also because underdetermined by the evidence.

Why does this matter? There are several reasons why one might wish to have a taxonomy of different kinds of “complexity” in cancer, and also, to know whether these features do important predictive and explanatory work. First, clarifying how talk of “complexity” among cancer researchers parts ways with other domains can prevent confusion (or rushes to judgment) about the import of cancer’s “complexity,” for both debates among scientists and philosophers about complexity, and for practical applications. Second, philosophical debates over whether cancer exhibits “emergent” properties, or “downward causation,” in part hinge upon whether some of these features of cancer do explanatory work.[[3]](#footnote-3) A necessary propaedeutic to resolving such issues is thus a careful look at the evidence. Third, a frank exploration of the challenges facing providing evidence for such claims provides useful insights into why many philosophical debates about emergence and reductionism seem to so often arrive at an impasse. Last and certainly not least, knowing of such relationships may have important clinical implications.

Regarding this last point, we have good reason to be cautious. Innovative approaches to cancer that incentivize interdisciplinary research have received generous funding of late (in part due to a deliberate funding plan from the U.S.’s National Research Council, which promoted an “information commons” and “knowledge network,” integrating data and methods from “genomics, proteomics, metabolomics, systems analyses, and other modern tools” (NRC, 2011)). There is thus an incentive to frame one’s work in the language of “systems,” and “networks,” drawing upon models and language from complex systems theory. In such a climate, we should be cautious to distinguish merely rhetorical versus substantive appeals to such theoretical terms, and particularly in considering claims to potential for directing these observations at development of clinical applications. Unfortunately, promises of clinical relevance are often made well before there is any clear evidence that such information can or will be useful, particularly in research with bearing on cancer (Ghannad, et. al., 2019; Boutron, et. al., 2018; Lazarus, et. al., 2013).

Recently, there has been an attempt to “integrate” or “tame” cancer’s complexity, advocated by Boniolo, et. al. (2019). In my view, integration – even the “clustered integration” they advocate – in this context, only captures or provides “order” to one sense of complexity in the cancer literature, genetic “heterogeneity.” Boniolo and Campaner hope for “a unitary framework to address complex diseases”; and advocate for integrative clustering of data as a method of classification of cancer types and subtypes. While this approach may be successful in “taming” the problem of cancer classification, this is only one dimension of cancer’s “complexity,” and one kind of challenge attention to complexity can solve. Attention to the distinctive and fine-grained ways in which cancers are spoken of a “complex” is essential to better understanding of cancer initiation progression, and potentially also, prognoses and treatment. Thus, before turning to how cancer is described as “complex” in the cancer literature, we should get our bearings regarding the consensus (such as it is) about what features are thought to be common to “complex systems,” or generalizations about how some such features tend to promote others. While talk of “complexity” and complex systems is enormously varied, to the extent that there is any consensus about such systems, it will be useful to familiarize ourselves with this consensus. Otherwise, it will be unclear whether cancer scientists’ discussions have any bearing on debates about complexity, more generally. That is, to determine whether cancers count as an instance of any *general* properties or relations thought to be characteristic of entities that are distinctively “complex,” one ought to begin with some sense of what those features are.

2.0 Defining “Complexity”

Which properties are distinctive of complex systems, as well as whether and why these features tend to travel together, has been a matter of some dispute since Herbert Simon’s 1962 *Architecture of Complexity*. In part, this is due to the fact that scientists’ definitions and measures of features like “adaptive behavior” or “organization” varies so much across disciplinary contexts. Even within any particular discipline, there can be disagreement about whether and in what sense a system exhibits features such as “adaptive behavior.” For instance, a point of particular contention in the context of biology is how best to explain and define features like “robustness.”[[4]](#footnote-4) Thus, any discussion of such features should be extremely sensitive to the way in which such a term is operationalized in the context at issue.

Philosophers of biology have endorsed a variety of more or less pluralistic views about what is distinctive of complex systems (Wimsatt, 1972, 2007; McShea, 1991, 2000, 2010; Bechtel and Richardson, 2010 (1993); Bedau, 2003, 2009; Mitchell, 2009; Bechtel and Abrahamsen, 2009). For instance, Mitchell (2009) identifies multiple kinds of complexity as typical of biological systems: “multilevel organization, multicomponent causal interactions, plasticity in relation to context variation, and evolved contingency.” She argues that complex biological systems have emergent properties, which she glosses as follows: “nonaggregative compositional structures, self-organization, nonlinearity, feedback,” and “higher-order properties with causal efficacy.”(Mitchell, 2009; 21, 32) On this account, biological systems may possess some or all of these features, and no one feature is necessary for taking a biological system to be “complex.” In contrast, Bechtel and Abrahamsen (2009) identify “cyclic organization and resulting oscillatory dynamics” as key elements of complex biological systems. These feedback mechanisms are, they argue, what gives biological organisms their distinctive “autonomy” or self-regulation; it is in virtue of such mechanisms that organisms are capable of recruiting matter and free energy, and deploying them both in service of construction and repair of components. McShea (1991, 2000), and McShea and Brandon (2010, 7), in contrast, take ‘complexity’ to mean “number of part types or degree of differentiation among parts”, and distinguish ‘complexity’ in this sense from “functional complexity.” Thus, “diversity and complexity” are one and the same thing on this view, and, the extent to which a system increases in heterogeneity (or, complexity in this sense) can be quantified in terms of Shannon entropy. Philosophers of biology thus seem to identify biological complexity with heterogeneity, and others with functional organization, autonomy, and self-regulation, and others still with the complex interplay between the two, where the former will tend over time to promote the latter.

Rather than take a stand on this contested issue here, I will for the purposes of this essay argue that “complexity” is a family resemblance term. By this I mean that complex systems do not make up a natural kind, at least in the sense that there are no “essential” features associated all and only with complex systems, or unique to such systems. Moreover, some features taken to be typical of complex systems may tend to promote others, but these are not exceptionless regularities. If you look to how the term is applied across the sciences, complexity is typically understood to be a matter of degree; so, while complexity is ubiquitous in the sense that some of the above mentioned features are found in many natural systems, highly complex systems like the human immune system, for instance, are rare. In other words, complexity (at least of high degree) is often taken to be a special accomplishment.

While different disciplines inquire into different aspects or features of complexity, there is an attempt at offering up a general theoretical framework for complex systems – “complex systems theory.” Complexity theorists model complex systems and their features, and give formal measures of various features of complexity; however, there is no agreement on these measures. [[5]](#footnote-5) Many things *can* be represented using the formal tools of complexity theory, but we may not wish to call all such systems “complex.” The expression “complex system” is typically reserved for systems that share many such features in common; no one feature is typically taken to be either necessary or sufficient. Ladyman and Wiesner (2020) describe several of these features, or, identify several widely accepted “truisms” about complex systems, including but not limited to generalizations about how such features are thought to be systematically related:

A system is complex if it has some or all of spontaneous order and self-organisation, nonlinear behaviour, robustness, history and memory, nested structure and modularity, and adaptive behaviour. These features arise from the combination of the properties of numerosity, disorder and diversity, feedback and non-equilibrium. (Ladyman, et. al., 2020, p. 16)

Of course, this is a very abstract, general description; different disciplinary contexts will require different specifications, and operationalizations, of “modularity,” and “robustness.” Nonetheless, the above is intended to accommodate the variety of ways in which complex systems are described and investigated across many different scientific domains. As they authors note above, the above features fall roughly into two general categories: (1) underlying causes of, or mechanisms for, complexity (e.g., numerosity, disorder and diversity), and (2) observable behavioral effects of complex systems (e.g., modularity, robustness, adaptive behavior). That is, Ladyman and Wiesner take themselves to be identifying features widely taken to be conditions on, or promoters of, others. For instance, systems exhibiting various kinds of feedback may have a greater tendency to exhibit “robustness” or “adaptive behavior”. By way of example, adaptive behavior in bacteria is in part a product of feedback mechanisms, such as quorum sensing.[[6]](#footnote-6) In the below table (Table 2), I describe how each of the several features listed by Ladyman and Wiesner may be exhibited in cancer.[[7]](#footnote-7) Let us turn to the cases at issue.

3.0 General Senses of Complexity in the Cancer Literature

One central challenge in analyzing discussion of “complexity” in the cancer literature is that it is not always made clear whether a given feature is taken to be indirect *evidence for* (i.e., a proxy of), *constitutive of*, or, perhaps, one of several *causes* of, “complexity.”[[8]](#footnote-8) I will do my best to specify in the below which of these is at issue, as well as identify some general regularities or associations between causes and effects. First, however, it may help to distinguish two general ways in which cancer is typically characterized as “complex” in this literature. First, and most commonly, cancer (either an individual tumor’s population of cells, a particular subtype, or the set of types and subtypes of cancer) may be referred to as “complex” in light of its *diversity* or heterogeneity.[[9]](#footnote-9) Second, an individual tumor, cancer type, or class of subtypes, may be referred to as complex in light of its *organization* (though of course, cancer is far from “organized,” there are “organizational” features of cancer signaling pathways, networks, or dynamics, or patterns of organization of such pathways and networks that are taken to be distinctively “complex”).

3.1 Heterogeneity

In the majority of cases in the cancer literature, the feature identified as indicative of cancer’s “complexity” is its sheer diversity, or heterogeneity.[[10]](#footnote-10) There is both “intra-“ and “inter-tumor” heterogeneity. That is, “heterogeneity” can refer to genetic, epigenetic, or gene expression variation among cells *within* an individual tumor, or relative extent of genetic, epigenetic, or other variation among cancers that share the same cell or tissue or organ, or extent of variation across different types or subtypes. That is, an individual tumor, or general type or subtype of cancer (e.g., ovarian cancer[[11]](#footnote-11)) might be characterized as highly “heterogeneous” – in the sense that it typically contains many (or more diverse) mutations within the population of cells that make it up,[[12]](#footnote-12) or more or less variation on average, relative to other cancer types. Talk of cancer’s “complexity” is not limited to sheer number and diversity of mutations typical of such a cancer type or subtype. It can also refer to extent of variation in *types* of alteration typically found within a cancer type, relative to other cancer types or subtypes (e.g., base pair changes, deletions, duplications, and inversions).

Yet another sense is the heterogeneity of cell types, molecules, or molecular complexes involved in either a tumor, or a cancer type or subtypes’ initiation and/or progression (e.g., leukocytes, fibroblasts)), heterogeneity of causal mechanisms underpinning the behavior of cancer cells, or diversity of functional pathways affected. Moreover, the extent of genetic or genomic heterogeneity is often taken as a proxy for the diversity of functional pathways affected. That is, various types of heterogeneity may be taken as either constitutive of, or proxy for, other types of heterogeneity. A more genetically heterogeneous tumor may be more likely to exhibit “complex” behavior (e.g., recurrence or resistance to therapy).

There are several reasons why genetic heterogeneity within and across cancers features so prominently in this literature. One rather mundane reason is that there has been such a vast investment in cancer genomics in the past several decades. This research is driven largely by the presupposition that cancer’s “hallmark” functions – the behavior of cancer cells – are “driven” by a com­bination of genetic mutations. Understanding how and why those mutations yield such behaviors will – it’s assumed – enable not only better understanding of cancer biology, but also development of “targeted” treatments. With insight into the molecular processes driving tumor progression, the hope is that one can better stratify patients in terms of their risk profile, and likely response to drugs, as well as develop treatments that intervene ‘precisely’ on those processes (Collins, et. al., 2007). One central aim of cancer research currently is to stratify heterogeneous populations of breast, lung, or prostate cancers into clinically meaningful subtypes as determined by similarity of molecular profiles. Though, while sometimes molecular data can result in stratification of further subtypes, at other times, such data challenge the classifications based on site of origin (at least for choice of treatment) – leading to cross-cutting classifications (Hoadley, et. al., 2014). Such stratification is thought to be essential to “personalized,” or “precision” therapies. Therefore, there is a great deal of attention in the cancer literature to documenting the extent (and nature) of genomic variation (or “heterogeneity”) within and across cancers of various types.

Of course, heterogeneity can only be ascribed to a population of entities – whether cells in a tumor, or populations of cancer types or subtypes (or genomic databases of these) – and is typically used as a comparative measure. That is, heterogeneity refers to a *relative measure* of variation found either within or between cancer types. For instance, smoking-associated small cell carcinoma of the lung is typically more genetically heterogeneous (bears more and more diverse mutations) than childhood leukemia (specifically AML) (Lawrence, et. al., 2013)). Where “heterogeneity” refers to the extent of genetic or genomic variation found *among cells or cell lineages within a single tumor*, the comparison is typically with other populations of cancer cells in a tumor of the same type, or earlier stages of the same tumor. Thus, for instance, an treatment resistant ovarian tumor typically bears more mutations than a treatment “naïve” tumor. The potential implications of this diversity are discussed further, below.

3.2 Organizational Complexity

The second general sense of “complexity” found in the cancer literature is a somewhat motley category. It covers a variety of functional and structural features of not only cancer cells and tumors, but also the tumor microenvironment, the immune and endocrine system, and signaling pathways within and between them. Though this term may not be ideal, I refer to this as “organizational” complexity, since many of the features identified have to do with organization of, or functional relations between, parts, processes, or signaling molecules, within and between a tumor and its environment. By way of example, the particular organization (or, reorganization) of signaling pathways that play a role in cancer initiation and progression in a particular cancer type or subtype may be described as “complex” in this latter sense, in that the network exhibits feedback, or redundancy.

While the category is a motley one, one can identify four general types of “organizational” complexity discussed in the cancer literature, and these are not mutually exclusive. One particular way in which the organization of causal processes involved in cancer are taken to be “complex” is that they span the tumor and stroma, or involve multiple systems (e.g., endocrine system, immune system, etc.).[[13]](#footnote-13) This is taken to be “complex” in that it involves causal relationships between several cell types, tissues, and often involves changes to the organization or regulation typical of such systems in healthy organisms. For instance, Lesterhuis, et. al. (2017), describe how the same feedback loops and modulatory factors that typically govern immune response can be coopted by a tumor to limit the success of immune therapy.

A second (related) example of this motley category of “organizational” complexity is when different outcomes are associated with different background conditions, or a regulatory activity, mechanism, cell, or whole collection of cells and tissues, behaves in a context-sensitive way. Of course, context sensitivity of this sort is fairly typical in biological systems, but it can become both a liability and a boon in cancer, depending (not coincidentally) on the context. For example, the same process (autophagy) might typically be involved in tumor suppression, and yet, autophagy inhibitors can act as anticancer therapies (Gómez, et. al., 2015). Such apparently “paradoxical” effects of the same process are often taken as instances of “complexity.” Another illustration of the same principle (which also happens to overlap with the feature of complexity identified above) is that various aspects of immune response can both promote and inhibit cancer, in a context sensitive manner (i.e., depending upon background conditions).[[14]](#footnote-14) The cellular plasticity is another example of context dependent behavior of cancer cells that is sometimes referred to as either *illustrative of*, or, a *cause of*, complexity. For instance, “stemness” is something that can be both “acquired” by tumor cells, and “lost,” – it’s not a fixed property, in other words, but one that is relatively plastic. This is often taken as evidence for either the “complexity” of such cells, or, a cause of “complex” behavior. That is, in this context, “complex” is being used as both cause and consequence: “plastic,” “context-dependent,” behavior is thought to yield greater adaptation, robustness, or resilience. See Table 1, where I refer to some examples of this relatively motley category of complexity.[[15]](#footnote-15)

Third, sometimes extent of “disorganization” of tissue architecture, vascularity, or disruption of chromatin (modification of histone architecture of the genome) is used as a tool for diagnosis of more or less aggressive forms of cancers. Such disorganization can be measured by tools, such as fractal dimension. Such extent of “disorganization” or structural modifications of what is typically found in functional organs or tissues may be taken to be an instance of “complexity” in an individual cancer, or cancer type or subtype (Tambasco, et. al., 2010; Metze, 2010, 2013; Taverna, et. al., 2009).

A fourth and last example of “organizational” complexity is one that draws explicitly on complex systems theory: signaling networks associated with cancer may exhibit various forms of feedback (cyclic feedback), and oscillatory dynamics. Signaling pathways associated with cancer may also exhibit scale-free architecture (networks with a few tightly connected nodes, and many nodes with very few connections). These organizational features of cancer are sometimes taken to be causally relevant to various outcomes of interest – e.g., adaptability, for instance, in response to viral therapy, or functional plasticity (Wodarz, et. al., 2009; Yarden, et. al., 2012; Bechtel, 2018).

Of course, the above categories are not mutually exclusive. The same cancer, cancer type, or subtype can be described as “complex” both in virtue of the heterogeneity of its parts in interaction and its organization, plasticity, adaptability, or resilience. Indeed, these features are often taken to travel together; where one or more such features is taken to promote others. Let us now consider exactly how such features are typically taken to not only characterize cancers as “complex,” but also do this predictive and explanatory work.

4.0 On What Complexity Explains: Heterogeneity

Let us begin with the most common or typical feature of cancer thought to be representative of complexity in cancer: “heterogeneity.” Why exactly is heterogeneity interesting or important? What predictions or explanations are typically made of such “heterogeneous” cancers? The variety of parts in interaction involved in cancer initiation and progression is often used as evidence for, or indeed a direct cause of either “robustness” to insult, or “adaptability.”[[16]](#footnote-16) Where there are many mutations (it is often assumed), a cancer will be more likely to exhibit diverse capacities (often, the “hallmarks” of cancer are referred as instances of these “capacities” – such as resistance to apoptosis, unlimited growth, etc.), and this diversity is taken to further potential for “adaptability”. A cancer with many alterations may, it’s thought, be better able to grow in diverse environments, invade neighboring tissue, metastasize, and respond effectively to attack from either the immune system, or medical intervention, such as chemotherapy. Why might this be so?

A single tumor might contain many different cells, variation among which may make differential contributions to the growth or invasion of a tumor, such as the capacity to attract a blood supply, break down epithelial barriers, invade and metastasize. Particularly advanced tumors (e.g., high grade glioblastoma) may contain diverse lineages or subpopulations of cells containing different subsets of mutations, as well as epigenetic alterations. These could in part be the product of a multiclonal origins; it is thought that, for instance, in some breast tumors, such heterogeneity may be in part a product of multiple “cancer stem” cells (cells undergoing continuous renewal) (Zhao, et. al., 2016). It is just this heterogeneity that is thought to enable a tumor to adapt to, or invade and survive within, novel environments, such as bone or brain. Here one need not be committed to the view that this is a process of natural selection (adaptation), or change in the distribution of variation in the population of cells over time.[[17]](#footnote-17) It may simply be that the possession of these properties enables such cells to be enormously plastic in their behaviors, and thus survive in a range of novel conditions.

Inter- and intra-tumor heterogeneity often go together, but they need not. The rationale for attention to heterogeneity in both senses is that more heterogeneous cancers are (by and large) assumed to be more difficult to treat. First, a more heterogeneous cancer type (e.g., high grade glioblastomas) may be more difficult to treat, perhaps because typically by the time such cancers are discovered, they are relatively advanced. Second, as mentioned above, extent of intra-tumor variation may enable the evolution of resistance to therapy. This is sometimes explained in light of the larger reservoir of mutations available for “selection” – or relative survival and reproductive success – among cells in a tumor. That is, more diverse populations of cancer cells in a tumor may be expected to possess variation in mechanisms that enable the cell to bypass the activity of various drugs. That is, diversity of mutations is taken to be associated with an overall greater evolvability, plasticity and functional complexity, in the same way that populations of organisms may be said to be more or less “evolvable” (Brown, 2014). Akin to explanations in classical population genetics, the thought is that a more heterogeneous population of cancer cells may also be thought to be more likely evolve resistance, given that there is more variation available for selection. Here there is variation in the presence or absence of mechanisms associated with, or promoting “resilience,” or “robustness” in response to various environmental insults.

What evidence is there of a causal relationship between genetic heterogeneity and evolvability, robustness, or indeed, adaptations or functional organization? First, it’s relatively uncontroversial that cancers evolve in the (minimal) sense that they are a population of cells that change over time in the distribution of frequencies of genetic and epigenetic variations. Some such changes can make a difference to the relative survival of descendent cells, and so may be characterized as a process of natural selection (Merlo, et. al., 2006; Greaves, et. al., 2012; Maley, et. al., 2017); though of course, surely some also are purely a product of “drift,” or chance survival of this or that lineage or subpopulation (Laplane et. al., 2018).

More controversial is the general claim that greater intratumor heterogeneity increases the chance of therapeutic resistance evolving, as a general rule. By and large, it is true that late stage tumors (and some cancers types or subtypes) have greater genetic heterogeneity, and also that they are more difficult to treat, but whether this is a causal relationship due to an evolutionary process is not something that has been studied experimentally (nor could it, exactly). What we have is indirect evidence from retrospective studies taking multiple samples of a tumor over time, and correlation of greater initial diversity with higher rates of recurrence and/or resistance. This is consistent with the in principle argument that more genetic variation available for selection means that a population can respond to selection more effectively, because it contains a reservoir of variation for selection to act upon. The indirect evidence for this causal link between heterogeneity and evolvability in cancer is pretty substantial (Greaves, et. al., 2012). Indeed, going back to the 1960s, oncologists have typically used a series of drugs in combination, rather than single chemotherapy drugs, exactly because cancers typically acquire resistance to single drugs in isolation. “Combination” chemotherapy (agents are used in sequence) has been shown to be effective against many of the treatable cancers – from leukemia, to breast, lung and prostate cancers. Much like the evolution of antibiotic resistance, cancers seem to eventually bypass one after another drug.

A second way in which a more heterogeneous tumor might be more “fit” is with respect to a property of the tumor as a whole: a tumor with a great deal of intratumor heterogeneity may *already* exhibit a great deal of *redundancy* of functional components (gene duplication events may play a role here, or a more diverse population of cancer cells may have different mutations performing similar functions). This redundancy is a kind of built in “preadaptation” to resistance. If a drug successfully intervenes upon one pathway or mechanism, another similar one with a slightly different way of achieving the same ends can bypass the effects of a targeted intervention. Whether or not this leads to changes in the distribution of frequencies of cancer cells with different genotypic or phenotypic properties, this ‘pre-adaptation’ is itself an way in which a more “heterogeneous” tumor is “resilient.” Another way of framing this same point is that we might expect a more heterogeneous “network of pathways” affected by a drug to exhibit “distributed robustness.” If, for instance, a drug works by knocking out a pathway associated with angiogenesis (generating a blood supply to the tumor), a tumor where multiple pathways are available to perform the same function may be more “robust.” While they may not all perform the same function with the same efficiency, they could be deployed when called upon. In this case, the *extent of division of labor and/or redundancy* in the system could be a measure of relative “fitness” at the level of the tumor as a whole.

A vivid example of a cancer that may be illustrative of the above is in ovarian cancer (Muinao, et. al., 2018). Cancers need vasculature to survive and grow. There are several different types of anti-angiogenic drugs, which block the growth of a blood supply, and have in the short term been effective in ovarian cancer (e.g. Avastin). However, within ovarian cancer, there can be redundancy of pathways associated with angiogenesis, associated with a particular tendency to be resilient to treatment. That is, when a drug “knocks out” one functional pathway, another (somewhat less efficient) pathway can take over this same function. That is, while many of the antiangiogenic drugs work at first, upregulation of redundant angiogenic pathways, or various compensatory or bypass angiogenic mechanisms, enable these tumors to continue to grow and progress to metastasis, even when treated with anti-angiogenic agents (Gacche, et. al. 2018). It’s possible that cancers with a greater degree of genetic instability and heterogeneity may be more likely to be resilient to therapies such as Avastin.

However, while the indirect evidence for this seems substantial, as mentioned above, another explanation for this correlation is that genetic heterogeneity may simply be an artifact of the stage or age at which such cancers are typically discovered. Moreover, it’s worth noting that the correlation between heterogeneity and robustness is not linear; not all cancers with very few mutations are necessarily easier to treat, or less likely to recur. Childhood leukemia is typically associated with relatively few mutations and chromosomal alterations (Lawrence, et. al., 2013). Yet, some childhood cancers prove incredibly tenacious. Thus, there are exceptions to the rule that “heterogeneity” or “numerosity” promotes “robustness”. Whether and how it does depends on exactly which mutations or alterations to the genome are involved, and exactly how they disrupt the behavior of cancer cells. All this is complicated yet further by the fact that genetic and epigenetic heterogeneity are not the only contributing factors to a tumor’s resilience and capacity for resistance.

For instance, Swartz, et. al, (2012) discuss the “complex” role of the tumor microenvironment (TME) in cancer. By this they mean that the microenvironment involves dynamic interactions between a diverse set of factors in the stroma surrounding the tumor, all of which (eventually) can contribute to the growth and invasion of a tumor, as well as resistance to therapies. They describe the TME as a “dynamic milieu”: tissue is “remodeled,” there are ongoing metabolic alterations in the tumor (dynamic changes in type of metabolism of cancer cells), and changes in the recruitment of stromal cells. A variety of immune cell types, typically involved in wound healing, are “recruited” – i.e. attracted to the stroma and activated in service of either the growth or invasion of the tumor, or enabling resistance to treatment. The TME is described as “educated” by tumor cells: “reciprocal interactions between the diverse assemblages of stromal cells and evolving neoplastic cells fundamentally regulate tumor progression. Adaptive and innate immune cells represent a significant component of the TME.” Pathways of communication between stromal and tumor cells are diverse, there are immunomodulatory roles of the lymphatic system, and contributions of the intestinal microbiota, both positive and negative, to tumor growth. This “heterogeneity” (of tumor microenvironment) is thus thought to shape the “ecology” and “dynamics” of cancer, though in different ways in different organs and tissues. So, genetic or epigenetic heterogeneity alone is likely not the exclusive, though possibly a significant, cause of robustness in cancer.

The hypothesis that there is a direct causal link between genetic heterogeneity and resilience thus faces two central challenges. First, for systemic or “higher level” features like “genomic diversity”, it is very difficult to demonstrate empirically that the former causes the latter, and there are so many other candidate confounding causes. At best, what we often have is a correlation between the two. Indeed, until relatively recently (Gerlinger, 2012), we did not have a single instance of a patient whose cancer we had followed over time, or from which we had taken multiple serial samples, so as to trace the trajectory of genetic and epigenetics changes in the population of cells in the tumor over time. When we do, moreover, the explanation for why and how variation helps or harms often varies with the cancer type and subtype. For instance, patient age (and thus incidence of acquired mutations in over the course of a lifetime in the precursors to white blood cells) is the main cause of genetic variation in AML (acute myeloid leukemia) (Welch, et. al., 2012). Given that age itself can be a confounding cause of poor response to therapy, it’s difficult to separate out the relative contribution of age and genetic variation to resilience.

Second, the extent and variety of heterogeneity, and its role in the evolutionary dynamics of a tumor, may be expected to vary across different tumor “environments.” Hausser, et. al., (2020) propose to extend ecological models – in particular, a multi-task “trade-off” model – to cancer. They suggest that – both given different kinds of challenges faced by cancer cells in different tumor microenvironments, and different challenges facing cancer cells at different stages, different “trade-offs” among competing optima may be at play in different cancers (e.g., cell division, biomass and energy production, lipogenesis, immune interaction, and invasion and tissue remodeling). Using this multitask model, they generate theoretical “archetypes” or models of such trade-offs, and they use genomic data to argue for different trade-offs between gene expression profiles in cancer, suggesting that there may be cancer “generalists” and “specialists.” In other words, according to Hausser, et. al., we can explain intertumor heterogeneity as products of various trade-offs unique to each cancer type, at different stages, and indeed, perhaps also, among different cells in a tumor whatever functions associated with such a type:

The archetypes also showed differential clinical properties ... Close to the invasion and tissue remodelling archetype are tumours from patients with a high number of lymph node metastases. Tumours with the highest histological grade — that is, the poorest tissue differentiation — are located closest to the immune interaction archetype in the gene expression space. Early- stage tumours are found closest to the cell division, biomass and energy production, and lipogenesis archetypes, whereas the immune interaction and invasion and tissue remodelling archetypes are located closest to late-stage tumours. This finding suggests that part of the intertumour diversity in gene expression is due to temporal changes in selection pressures during tumour progression, in which interacting with the immune system and invading surrounding tissues become increasingly important over time. (Hausser, et.al., 2020, 248).

According to Hausser and Alon, then, “heterogeneity” is not as a general rule (or at least not necessarily) a direct contributor to “adaptability,” “resilience,” or capacity to evolve resistance to various insults. Instead, it’s a highly context-dependent resource: given the particular cancer stage, as well as the context in which a given cancer happens to be growing, extent or variety of genetic heterogeneity may be more or less optimal. Hausser and Alon describe particular trade-offs facing cancer cells in their particular, local microenvironment, in response to local microevolutionary pressures. That is, they are emphasizing how uniformity of genomic profile may be optimal for growth and invasive capacity, in some tumor microenvironments.

In sum, even though in principle we might as a general rule expect more genetically heterogeneous tumors to be more difficult to treat, this is not an exceptionless generalization. Not all mutations have the same significance, and so not all heterogeneity enhances “fitness.” All cancers have some “passenger” mutations that make no functional difference to the behavior of cancer cells. Such mutations are neutral with respect to the “fitness” of the cancer cells, or have no effect on a cancer’s ability to invade, metastasize, or, for that matter, evade chemotherapy. Moreover, it’s quite possible that a genetically homogeneous cancer is distinctively difficult to treat – perhaps because it possesses a particular feature that enables it to bypass almost any attempt at treatment, or its growth is so rapid or uncontrolled that even the most toxic drugs seem unable to halt it.

Again, by way of example, consider AML. Leukemias by and large should (in principle) be easier to treat, if we assume that lower somatic mutation burden makes a cancer easier to treat. But, even though there are some AML patients do well on standard chemotherapy, and others do very well on a specific targeted therapy, there is an intermediate class of patients that have wildly different responses to chemotherapy and a variety of targeted therapies. Why this is the case is uncertain, but it may have to do with particular types and subtypes of mutation associated with these cancers (Ley, personal communication, 2018). So, the advantage of heterogeneity seems a highly context sensitive matter. Indeed, it suggests that what matters to cancers’ resilience may often have more to do with what I’ve referred to as “organizational” features of a cancer.

4.1. Organizational Complexity

There are, as mentioned above, at least four different senses in which cancers are spoken of as “organizationally” or “interactively” complex. For the sake of space, let us focus here on network organization as an example. Several cancer scientists (Huang, 2009, 2011; Kitano, 2004a, 2007) argue that there are “entrenched” gene regulatory networks, acting both in cancer and development. Moreover, they claim that there are distinctive kinds of signaling networks activated in cancer, associated with various outcomes, such as greater or lesser robustness (or capacity to survive, grow, and metastasize, even in the face of environmental perturbances, such as chemotherapies). They also argue that cancer’s dynamics exhibits the kind of “metastable” features characteristic of complex systems, arguing that these dynamics can be modeled using Waddington’s epigenetic landscape. On this view, we ought to think of the progression of a cancer as exhibiting the emergence of a “new” “stable” or “robust” homeostatic forms of network organization, more or less resilient to insult (e.g., from the immune system, chemotherapy, or biological agents).

The in principle arguments for the significance of distributed robustness as typical of biological systems are as follows. Wimsatt (1972, 2007) and Wimsatt and Schank (1988) have argued that organisms lack the orderly “hierarchical” organization and near-decomposibility Simon thought typical of complex systems, because evolution leads to “tinkering” and reuse of the similar parts for new purposes. Thus, the way in which organisms are organized may deploy the same or similar modules for different purposes, such that otherwise “discrete” modular parts may come to have multiple functions. Cancer’s network complexity – the kinds of organization we see where only a few “nodes” in the network tend to exhibit many interconnections – are in many ways derivative of the typical organization of cell signaling networks in healthy cells. That is, the pathways activated in cancer are often the same pathways active either in development, or wound healing; the behavior of cancer cells, such as unlimited growth, invasive capacity, ability to attract a blood supply, are in part due to alterations of these pathways. Some have argued that the networks that are activated in cancer are akin to “attractor” states or stable states of , typical of earlier stages of development, where cells are more actively dividing and differentiating (see, Huang, et. al., 2009, Huang, 2011).

There is ample indirect evidence that the networks activated in cancer are often (but not always) active states that are typically suppressed during ordinary development. Indeed, this is exactly the reason why cancer is often referred to as a kind of “reversion” of development: cancer cells often exhibit re-activation of processes typically silenced in the gradual differentiation and functional specification of cells and tissues (Barbletz, et. al., 2018). And, there is indirect evidence that organization of a network of signaling pathways is strongly associated with the “stability” of a state (or tendency to be difficult to dislodge from this state).

There are some examples of experimental attempts at finding evidence that certain *structural or organizational features* of signaling networks in cancer do predict and explain facts about cancer’s adaptability and resilience. For instance, Breitkreutz, et. al., (2012) attempt to demonstrate how certain network structures are more or less “robust” or resistant to insult. This would count as an instance of an “emergent” causal property, in that they are arguing that certain kinds of topological organization (in particular, scale-free organization) of networks lead to different outcomes (greater survival, or resilience, e.g., to chemotherapy) (cf. Huneman, 2010). They found a correlation between cancers whose networks “have the highest degree-entropy” and lower probability of 5-y survival in patients with such signaling pathways affected in their cancers. Network entropy, specifically degree-entropy, is defined as the sum of a multiple of the number of lines connecting nodes in a network. Overall they found that “cancers that have a more complex molecular pathway are more refractory than those with less complex molecular pathway,” where complexity was measured in two ways: the number of connections between nodes, and the extent of “centrality” of a node. The rationale behind using this measure as a tool for predicting mortality is as follows:

Scale-free networks are built from collections of a large number of nodes with a small number of connections, and a small number of nodes with a much larger number of connections. The fact that so many networks are scale-free (and actually, such a wealth of diverse phenomena in nature appears to be scale-free) results in some controversy concerning the meaning of scale-free networks in molecular biology … These networks are metastable dynamic systems that could, given the right perturbation, either transition to a different state or collapse entirely. This … is a result of the large-scale organization of these networks; they are small-worlds or scale-free networks (19). This topology results in networks that are both robust to attack and yet have key nodes that can cause the entire dynamical system, represented by the network, to collapse (20). (Breitkreuz, 2012, 9210)

In other words, networks of signaling pathways in cancers with a scale free architecture might exhibit dynamics over time that make them more robust. A more complex cancer (measured by “degree entropy”) might be expected to be more robust, and, this is what they found.

There are several other examples of “organizationally” complex features of cancer apparently yielding greater plasticity or adaptability of cancer cells. For instance, consider the case of NF-κB signaling pathway. This pathway is affected in many cancers, and it has both “pro-“ and “anti-“ tumorigenic effects, depending on various background conditions (Hoesel, et. al., 2013). This is sometimes referred to as a “paradoxical” aspect of the pathway, but from the perspective of systems theory, it becomes far less paradoxical. For, the genes and signals associated with this pathway form a highly connected “node” – i.e., the pathway has a great deal of “crosstalk” with other signaling pathways within and between cells, as well as a variety of complex feedback circuits associated with fine-tuning its response to upstream activators, and thus, downstream effects. Thus, the structural organization of the network does important causal and explanatory work. It is the organization and activation of the network that explains why, for instance, “inflammation in general and NF-κB in particular have a double-edged role in cancer” (Hoesel, 2013, p. 5). On one hand, the pathway is activated as part of immune defense, which can lead to the elimination of transformed cells (i.e., cancer cells). Yet, the pathway may also be activated in many types of cancer cells, and can promote up-regulation of activity of genes typically silenced, leading to the growth of a cancer. These tumorigenic activities appear to be highly context dependent, being more active in some cell types than others. Thus, “knocking out” activity in this network may vary in effectiveness at killing cancer cells. Arguably, this is a case where the organization of a network is doing explanatory work, shaping either robustness or vulnerability.

By way of a concrete example of how network organization can explain differential response in tumors to chemotherapeutic agents, consider the case of Lee, et. al.’s (2013) experiment using triple-negative breast cancer (TNBC) cells (discussed in Green, et. al., 2018). Lee, et. al. exposed the cells to different combinations of signaling inhibitors (erlotinib, an inhibitor of EGF receptors) and DNA-damaging agents (doxorubicin), to optimize apoptosis (cell death, a goal in cancer treatment), using time-staggered applications. They found that giving erlotinib several hours before doxorubicin increased apoptosis several fold, compared to giving erlotinib alone, doxorubicin alone, or erlotinib after doxorubicin. Using a mathematical network analysis, they were able to explain how this greater effectiveness came about; the process of applying erlotinib early shifted the “network organization” of the signaling pathways – i.e., “unmasking of suppressed proapoptotic pathways” led the cells to be more susceptible to the DNA damaging drugs.

The larger question at issue in much of the literature on complexity is whether this kind of phenomenon points to a general causal relationship between “signaling architecture” and “robustness,” or only local, highly contextual ways in which networks or pathways can exhibit greater or lesser resilience. Most cancers deploy core cell signaling pathways associated with functions typical of healthy cells – development, wound healing, cell repair, and growth (or cell division). And many pathways for such key functions in the cell tend to have a scale-free structure. But, this should not surprise us. After all, key pathways in the healthy development and regulation of cells are products of our evolutionary history, and so an architecture that is “robust to insult” may well be a byproduct of this history, and only indirectly a cause of “robustness” in cancer. It’s no mystery that it’s these very same mutations and signaling pathways that play key functional roles in cancer cells are “hubs” in scale-free networks, if indeed scale free networks are common products of selection for relatively robust cellular function in development, wound healing, and cell repair. Because such networks already exist in the cell, cancers tend also to have scale-free signaling network architecture. That they also play causal roles in the robustness of a tumor is – as it were – a “fortuitous” byproduct (at least from the perspective of the tumor, though not of course the organism!).

5.0 Generality of Complexity: the Philosophical Impasse

As mentioned above, it’s often taken to be the case that some features of complex systems tend to promote others: numerosity, disorder and diversity, feedback and non-equilibrium are features of systems that tend to give rise to spontaneous order and self-organization, nonlinear behavior, robustness, and adaptive behavior. Typically the latter are referred to as “emergent” properties, though of course, scientists and philosophers do not always use these terms consistently, either within or across various domains of research (cf. Mitchell, 2012). What conclusions can we draw regarding whether – as is often assumed – some properties typically associated with complex systems tend to promote other such properties? Can cancer serve as a special case of this more general claim?

First, the central reason philosophers have often been troubled by these questions is a concern with “downward causation” and relatedly, “emergent” properties. If, for instance, there are higher level generalizations to be discovered about the “upper level” property of network organization, such as, that we can predict that scale-free networks are more resilient, then this may seem to be an instance of “downward” causation, or, an “emergent” property. These properties are characterized as “emergent” because they seem to be relatively independent of “lower level” “realizations.” The reason why is that it is taken to be a feature of the organization of the network per se, not the realizers – or particular molecular signaling pathways that instantiate such networks – that cause “resilience,” or resistance to chemotherapy, for instance. Woodward (2020) describes the conditions under which such a picture might work; for the sake of brevity, I paraphrase his view as follows. Imagine that there is a higher level variable (such as temperature) that is multiply realized by lower level realizations (e.g., in different gases). He’s not suggesting that a change in the higher level would induce not change in lower level instantiations. Rather, we take a higher level variable to be “downward” cause on lower level variables when interventions on that variable change the value of some effect variable E, in a uniform way, independent of which among several lower level realizations of the higher variable holds. That is, changes of lower level instantiations are irrelevant to some outcome E, *conditional on* changes in the upper level variable. This is an instance of what some scientists refer to as “decoupling” or “separation of scales.”

Do we find instances of this in cancer? I have argued that while the evidence is suggestive in some cases, demonstrating that these higher level features of a tumor as playing a causal role that is decoupled from the lower level can be difficult to achieve experimentally. For instance, consider the example of Lee, et. al.,’s (2018) research above. Recall that they used different timings of application of a combination of drugs, (erlotinib and doxorubicin), and attributed the success of one sequence of applications to a shift in the network organization of the signaling pathways. On the one hand, this would seem to suggest that the outcome is conditional upon structural organization or network structure of the signaling pathways, not any particular features of the “lower level,” but a closer look suggests a more “fine grained” explanation: “unmasking of suppressed proapoptotic pathways” led the cells to be more susceptible to the DNA damaging drugs. That said, the system level features of the signaling networks provide clues to which kinds of intervention, as a general rule, are likely to be successful.

Whether scale-free architecture of signaling pathways involved in cancer is a cause of robustness in general, however, is difficult to assess. It’s not something we can test directly, at least not in situ. Nonetheless, there are *associations* between such network organization and the resilience of tumors, that are at least suggestive of a causal relationship. Some philosophers have found such examples of complexity in the biological world as providing evidence for not only complexity, and emergent properties in biological systems (Bertolaso, 2016). Whether or not we want to call such observations instances of “emergence” depends on whether we are relatively permissive or restrictive about what makes some state of affairs “emergent”. A weak condition is that whole systems (collectives) display properties that their parts do not. This condition is met by everything from the behavior of a gas to our solar system. A stronger condition is “self-organization,” “collective behavior,” or the emergence of adaptations. It’s not clear the instances discussed above meet this latter condition. In part, this is because the conditions on what we count as self-organization or adaptation are contested, and in part because some of the features described above may only accidentally be associated with the effects we see.

Assessing these questions is complicated by the fact that many such pathways that are activated in cancer are themselves products of evolution, and so have likely been shaped by centuries of evolutionary selection for redundancy and resilience. Thus, many candidate causal variables – such as the organizational features of genetic networks – were simply “inherited” otherwise functional cell signaling networks in health cells and tissues. That some such networks are scale free, or have a few nodes with a high number of connections, may or may not count as a special case of emergence *unique to cancer*, per se. After all, they may simply be recycled features of pathways and networks inherited from healthy cells and tissues.

In sum, there are a variety of features of cancer that are taken to be illustrative of its complexity. Some such features may indeed promote others, but the evidence is often correlational. As in many other contexts where philosophical debates continue to rage about complexity and emergent properties, the problem may be a matter of how we define our terms, or a matter of how evidence underdetermines our conclusions. In other words, we might draw a general lesson from the case of cancer. Drawing generalizations about how certain properties (network organization) promote others (robustness, adaptability) in complex systems is difficult, at least in part because experimental manipulation of “systemic” features like signaling pathway organization is so challenging. This underdetermination problem may explain why the debates in the philosophical literature on emergence and reduction so often seem at an impasse.[[18]](#footnote-18)

Another reason, however, is that talk of “emergence” varies quite significantly between scientists and philosophers. There are a variety of different ways in which “complexity” and “emergence” are used in the philosophical literature, and they do not map in any direct way onto the ways that such terms are typically understood by scientists (Mitchell, 2009, 2012; Green, 2018; Bedau and Humphreys, 2008). For instance, Kim argues that downward causation would result in causal overdetermination (e.g., Kim 1998), and so, higher-level causation and downward causation either collapse into lower-level causation or result in a violation of the physical laws that apply to lower-level constituents (Kim 2000). This notion of downward causation and associated views of “emergence,” however, is different from what scientists by and large have in mind (Green, 2018). What Kim calls “the intuitive idea of an emergent property… a purely physical system, composed exclusively of bits of matter, when it reaches a certain degree of complexity in its structural organization, can begin to exhibit genuinely novel properties not possessed by its simpler constituents” seems closer to the talk of emergence at work in discussions of cancers’ complexity. That is, the sorts of features and behavior that scientists are interested in are not instances of causal overdetermination, or “downward causation” as Kim (rather narrowly) understands the expression (2006).[[19]](#footnote-19)

The sorts of downward causation of interest to cancer scientists are, instead, either examples of what Green (2018) calls “top-down effects as operating via constitutive or constraining relations given by the boundaries and organization of the system as a whole,” or what Woodward (2020) calls “separation of scales” or decoupling”. As we’ve seen, there are a range of examples of “complex” features of cancer cell populations, cancer types, or individual tumors. Whether, and how features such as this – network organization, for instance – constrains change, or decouples from the lower level – is enormously difficult to demonstrate empirically. Woodward makes it a condition of his account, for instance, that we must be able to demonstrate conditional independence of these higher level variables (Woodward, 2020, p. 853). It would, presumably, be quite difficult to demonstrate this experimentally – a fact which Woodward himself grants. These sorts of ideals for evidence may in part explain the way claims about higher level causation have seemed so often to fail to achieve the attention – let alone widespread scientific consensus – they perhaps deserve.

6. Conclusions

The aims of this paper have been twofold. The first is a descriptive project. I’ve argued here that the notion of “complexity” is not used univocally across different contexts in the cancer literature. Moreover, I found that in the majority of cases, genetic or genomic heterogeneity received the greatest attention. Indeed, it is often identified as either key evidence for, or indeed more or less identical with, cancer’s “complexity.” In the category of “organizational” forms of “complexity,” researchers could be referring to number or type of interactions across different spatial or temporal scales (genomic, protein, and tissue) or across different systems, (e.g., across tumor and immune system), structure of signaling networks or pathways, morphological features, such as tissue disorganization, context-dependent or highly plastic behavior of cells or whole tumor micro-environments, or organization or reorganization or networks of signaling pathways that contribute to “macro-“ scale outcomes such as drug resistance.

Second, I examined whether there was evidence in support of the claim that some of these features tend to promote other such features. I found that indeed there is broad support in the cancer literature at very least for the general hypothesis that more genetically or otherwise heterogeneous tumors might be *expected* to be more resilient to therapy. However, whether intratumor heterogeneity is a cause or effect of seems to be an open question, or at very least subject to exceptions, if considered as a general rule. I have also argued that the evidence for claims about the structure or network organization of signaling pathways associated with higher level properties is suggestive, but not decisive. The structural organization of signaling pathways in cancer can certainly play an important role in constraining plausible mechanistic explanations, or explaining context-dependent effects of other factors, such as drugs or inflammatory response. Whether as a general rule signal pathway organizations are causes of general features of a tumor, such as robustness to insult, however, is difficult to demonstrate experimentally.

The core issue at stake in many of the debates about whether examples such as those above in cancer illuminate irreducible macro-level causal properties, in other words, is often underdetermination. While we may find correlations between, e.g., systemic organizational properties of signaling pathways and various outcomes, it is very difficult to show that one led to the other in cancer. Scientists may demonstrate that structures of certain types correlate with an effect of interest, but whether the structure or organization in these cases doing genuine causal work is often underdetermined. This is perhaps one of the central reasons why many philosophical debates about reduction and emergence in the biological sciences seem so difficult to resolve. Indeed, it seems diagnostic of many philosophical debates about causation, explanation and reduction; exactly because terms such as these are not uniformly operationalized, and we cannot experimentally intervene in ways that decide such empirical questions unambiguously, the debate ultimately hinges upon in principle possibilities, or (on the opposing side) appeal to standards of evidence that are simply impossible to meet. For instance, one can imagine critics of Woodward’s approach to downward causation resisting the very possibility, exactly because establishing these kinds of conditional claims is so difficult. So, even if in principle possible, many skeptics doubt that such higher level causes are “actual.” It is always possible to invoke impossible standards of evidence in service of the remote possibility of reductive explanations, leading to an impasse.

In the case of cancer, it is very difficult to hold fixed, or, alternatively, intervene on, “system-wide” features, at least *in situ*. Often the best one can do is retrospectively establish correlations between various outcomes of interest and likely causes. When such correlations are robust (strong), and predictive, and we have good independent theoretical reasons to think there is such a causal and explanatory relation. While philosophers may remain skeptical, many scientists seem perfectly willing to grant that there are “higher level” causes, or perhaps “decoupling” of scales (Woodward, 2020; Green, 2018). But, some are unwilling to go this far, requiring something akin to experimental demonstration or manipulation where confounding factors are held fixed. This standard of evidence, arguably, lies a least in part at the base of disputes about whether, for instance, we ought to focus our attention in cancer research on molecular factors we can directly manipulate. Perhaps is it simply due to the fact that researchers use the “tools for the job” on hand; those that they know how to manipulate in laboratory and clinical settings. Yet, there are some potentially clinically relevant implications of thinking of tumors as a whole as having properties that potentially contribute to robustness, such as whether multi-task evolution contributes to the expression profile of a tumor, or whether organizational features of signaling networks or tissue architecture play an important predictive role in response to therapy. Thus, while (some) philosophers may remain unmoved by claims about system-wide properties doing causal work because their standards of evidence make it literally impossible to demonstrate the work of such properties,[[20]](#footnote-20) cancer researchers and clinicians might wish to go ahead and apply such insights in developing therapies, or in assessing diagnoses or offering prognoses.

To be sure, there are several questions to keep in mind when reading a paper purporting to offer examples of such phenomena in cancer. Rushing to judgment in such cases can have problematic, if not perilous, consequences. Particularly when considering clinical applications, however suggestive an association, theoretical model or simulation might be, it’s important to question whether the patterns are merely suggestive, or whether there’s more substantive evidence of a causal relationship. When applying such insights, we also need to move back and forth between the high level systems patterns, and context in which they are realized. Sometimes the fine grained causal details of which mechanisms are disrupted and how may matter quite a bit, if we wish to bring such patterns to bear in the clinical context.

How much does taking a “complex systems” perspective on cancer help, or matter? Building a theoretical model that fits data is easy; and, information about patterns or quantitative generalizations across cases are just that - patterns, not necessarily knowledge of processes. Detailed knowledge of process can matter a great deal to applications in clinical medicine. Thus, unpacking the evidence and discerning causal process would be ideal, certainly in advance of attempts at clinical applications. In lieu of this, there are theoretical models, simulations, and controlled experiments in isolated systems that nonetheless seem to suggest such complex features of cancer. Such features are deserving of greater philosophical attention, and may indeed have clinical relevance.

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1. For detailed discussion of the methodology of the search through the literature, please see notes to Table 1. [↑](#footnote-ref-1)
2. Complex systems theorists have argued that there are “higher-order laws” that govern complex systems, and evolved biological systems in particular (for a review, see Green, 2015a). Some argue that certain kinds of regulatory feedback, such as bi-stable switches, make such systems more resilient to insult, and more “evolvable.” (For further discussion, see, e.g., Green, 2015a, 2015b; Wolkenhauer and Green, 2013; Hooker, 2013; Kitano, 2004a, 2004b, 2007; Alon, 2007, Tyson, Chen and Novak, 2003). [↑](#footnote-ref-2)
3. The following are just a sample of the main contributors to this literature: Soto and Sonnenschein, 2005; Malaterre, 2007; Bertolaso, 2009, 2016; Green, et. al., 2018; Green, 2021. The term “emergence” is, needless to say, contentious (see, e.g., VanGulick, 2001 for discussion). Addressing whether and how cancer per se exhibits emergent behavior deserves further discussion; this paper is intended as a preliminary first step to addressing such a question. [↑](#footnote-ref-3)
4. For a review, see, e.g., Boniolo, et. al, 2017; and earlier, Wagner, 2007. [↑](#footnote-ref-4)
5. For a discussion of these measures, and their various merits, see Chapter 4 of Ladyman and Wiesner (2020). (While I am relying here on Ladyman and Wiesner’s list of features for the sake of economy (and their attempt at being comprehensive) in *What is a Complex System?,* there are of course other excellent reviews of this literature of complexity and complex systems (see, e.g., Wolkenhauer and Green, 2013; Green, 2015a, 2015b). [↑](#footnote-ref-5)
6. Quorum sensing is one of the simplest forms of feedback loop, found in a diverse array of bacteria, in service of everything from avoiding toxic environmental conditions to seeking food (see, e.g., Eickhoff, et. al., 2018) [↑](#footnote-ref-6)
7. Of course, whether these features and their co-occurrence are representative of these general regularities is exactly the matter at issue. I do not here claim to settle these issues once and for all, as these are empirical questions. [↑](#footnote-ref-7)
8. As mentioned in footnote 2, above, in many cases, scientists are simply referring to cancers’ “complexity” in the *subjective* sense that cancers are difficult to investigate and understand. I have made an effort to exclude where possible any such uses in my analysis, and focus only on objective features of cancer itself taken to be indicative of, or contributing to, “complexity.” [↑](#footnote-ref-8)
9. For, Ladyman, et. al., “numerosity” refers to many parts *in interaction*, not simply that a system has many parts. However, many cancer scientists simply use the term “complexity” more or less interchangeably with “heterogeneity,” which (as will be discussed further below) may refers to either the diversity of cancer types, diversity of parts or causal bases of a cancer or cancer type, or, both “inter-“ and “intra-“ tumor heterogeneity, and only sometimes the extent of interaction between these parts. [↑](#footnote-ref-9)
10. See Table 1 for methods. [↑](#footnote-ref-10)
11. For the purposes of this paper, I follow the majority of cancer researchers in typing cancers in light of the tissue or organ of origin (breast, lung, etc.). [↑](#footnote-ref-11)
12. Though, of course, not all mutations are “drivers” – or make a contribution to the behavior of a cancer cells; some are probably functionally irrelevant. This is of significance to the explanatory power of heterogeneity; some cancers of the same type (e.g., breast cancer) exhibit a long-tail distribution of mutations, with no mutation necessarily highly frequent, let alone present in all instances. [↑](#footnote-ref-12)
13. One might wonder whether this is different from “numerosity,” since it refers to multiple parts or processes. However, I place this in the category of “interactive” or “organizational” complexity because it refers to types of interactions that span multiple types of cell, or lead to activation of interactions between systems that typically exercise discrete functions. (Thanks for this question from Bechtel.) I take it that this may be assimilated roughly to what Mitchell identifies as “multilevel organization,” or “evolved contingency.” [↑](#footnote-ref-13)
14. For a much fuller discussion than is possible here, see chapter 4 of Pradeu, 2020. [↑](#footnote-ref-14)
15. Highly “plastic” entities or mechanisms are ones that can be modified to perform different functions, or revert to different states. Functional pleiotropy is when same function (chemotherapy resistance) is performed by a variety of different entities or mechanisms. This may be assimilated (roughly) to what Mitchell calls “plasticity in relation to context variation.” [↑](#footnote-ref-15)
16. I am not here taking these terms to be necessarily interchangeable, but simply listing or describing the “patchwork” of ways in which such features are described by cancer scientists. For a fuller discussion of this perspective, see, e.g., Boniolo (2019) for discussion of this “patchwork narrative” in cancer research. [↑](#footnote-ref-16)
17. As one reviewer helpfully points out, some cancer scientists are committed to this being a process of natural selection, but of course not all are. [↑](#footnote-ref-17)
18. Green (2015b) distinguishes two kinds of underdetermination that make reverse-engineering complex systems – and thus testing hypotheses about their properties – difficult. She calls these “synchronic and diachronic underdetermination.” Inferring to what systems theorists call “design principles” of complex systems is difficult, in other words, because “synchronic relations between lower-level processes and higher-level systems capacities are many-to-many,” and because “relations between system capacities and lower-level mechanisms are changing over time.” Both forms of underdetermination, arguably, are at work in the case of cancer. Perhaps related especially to this second sense, we might characterize a third type of underdetermination at work in the case of cancer: historical underdetermination. Namely, inferring facts about causal processes is made difficult because they have already occurred, and so we only have traces of past events as evidence. [↑](#footnote-ref-18)
19. Kim’s difficulties with the what he calls the “classical” conception of emergence are that the emergentist cannot consistently assert both that some macrostate supervenes on a microstate, and that it and its “emergent” features are irreducible to a microstate. For, whatever a supervenient property explains, its supervenience base could also explain, because whatever causal and explanatory work a purportedly emergent property can do, its supervenience base could equally well do. [↑](#footnote-ref-19)
20. See Green (2015b) for a detailed discussion of underdetermination in the context of “reverse engineering” and testing various hypotheses about network and system-wide structural properties of complex systems. [↑](#footnote-ref-20)