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Standard aberration: cancer biology and the modeling account of normal function

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Abstract

Cancer biology features the ascription of normal functions to parts of cancers. At least some ascriptions of function in cancer biology track local normality of parts within the global abnormality of the aberration to which those parts belong. That is, cancer biologists identify as functions activities that, in some sense, parts of cancers are *supposed* to perform, despite cancers themselves having no purpose. The present paper provides a theory to accommodate these normal function ascriptions—I call it the Modeling Account of Normal Function (MA). MA comprises two claims. First, normal functions are activities whose performance by the function-bearing part contributes to the self-maintenance of the whole system and, thereby, results in the continued presence of that part. Second, MA holds that there is a class of models of system-level activities (partly) constitutive of self-maintenance members of which are improved by including a representation of the relevant function-bearing part and by making reference to the activit or/activities which that part performs which contribute(s) to those system-level activities. I contrast MA with two other accounts that seek to explicate the ascription of normal functions in biology, namely, the organizational account and the selected effects account. Both struggle to extend to cancer biology. However, I offer ecumenical readings which allow them to recover some ascriptions of normal function to parts of cancers. So, although I contend that MA excels in this respect, the purpose of this paper is served if it provides materials for bridging the gap between cancer biology, philosophy of cancer, and the literature on function.

Keywords Normal function · Cancer · Philosophy of biology · Modeling · Pragmatism

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Introduction

Cancer biology features the ascription of normal functions to parts of cancers. At least some ascriptions of function in cancer biology track local normality of parts within the global abnormality of the aberration to which those parts belong. That is, cancer biologists identify as functions activities that, in some sense, parts of cancers are *supposed* to perform, despite cancers themselves having no purpose. The present paper provides a theory to accommodate these normal function ascriptions—I call it the Modeling Account of Normal Function (MA). MA comprises two claims. First, that normal functions are activities whose performance by the function-bearing part contributes to the self-maintenance of the whole system and, thereby, results in the continued presence of that part. Second, MA holds that there is a class of models of system-level activities (partly) constitutive of self-maintenance members of which are improved by including a representation of the relevant function-bearing part and by making reference to the activity or activities which that part performs and which contribute(s) to those system-level activities. Following Godfrey-Smith (2006, 2009b) and Levy (2015), I take models to be representations that abstract and idealize features of what they represent—their targets—with a view to predicting or explaining the behavior of those targets. A consequence of MA is that normal functions are primarily an explanatory kind, ascribed by biologists with a view to getting a grip on standard part-level causes of system-level phenomena of interest and, in the case of cancer biology at least, devising effective clinical interventions. That is, in the case of cancer biology, the point of identifying standards for some activity among a type of trait and within a type of cancer is to devise ways of undermining that activity to slow or stop disease progression. The claim that normal functions are explanatory kinds places MA within a pragmatist tradition in the philosophy of biology concerned with function ascription (Hardcastle 2002; Laubichler et al. 2015; Keeling et al. 2019). I contrast MA with two other, more purely metaphysical accounts that seek to explicate the ascription of normal functions in biology, namely, the organizational account and the selected effects account. It turns out that both struggle to extend to cancer biology. However, I offer ecumenical readings of modified forms of each which allow them to recover some ascriptions of normal function to parts of cancers. So, although I contend that MA excels in this respect, the purpose of this paper is served if it provides materials for bridging the gap between cancer biology, the philosophy of cancer, and the literature on function.

In the "Desiderata on descriptive accounts of function and normal function" section, I briefly discuss function pluralism and introduce two desiderata on what are sometimes called "descriptive" accounts of function. "The ascription of normal functions to cancers" section presents a representative example of cancer biologists ascribing a normal function to a part of a type of cancer. "The modeling account of normal function" section introduces MA and applies it to the example presented in "The ascription of normal functions to cancers" section. The "Assessing other accounts of normal function" section contrasts the success

of MA in satisfying both desiderata relative to normal function ascription in cancer biology with the other two accounts. I consider two objections to the claim that cancer biologists ascribe normal functions to parts of cancers in the "Objections: loose talk and going wrong" section before concluding with a comment on the philosophy of biology in the "Conclusion" section.

Desiderata on descriptive accounts of function and normal function

Function and pluralism

In this section, I briefly discuss the state of the function literature in the philosophy of biology (for extensive overviews, see Wouters 2005; Garson 2016) and introduce two desiderata on any account of function that seeks to explicate its ascription in biology. Function ascription is pervasive in biology. Following Weber (2017, 4744–4746), who generalizes from Cummins (1975)'s causal role account (see also fn.7), functions are, to a first approximation, activities[1] that parts[2] of biological systems perform and whose performance contributes in some way to those systems. To take the philosopher's favorite example, the function of the heart is to pump blood. This ascription tells us, first, that hearts pump blood and, second, that pumping blood contributes in some way to biological systems with hearts, for instance, by helping transport nutrients and waste to and from various tissues in the body. Ascribing a function explains by drawing our attention to the dispositions and/or structural features of systems that are causally relevant for system-level phenomena of interest. Biologists are keen to understand how or why biological systems persist and propagate. Functions indicate how those systems do so or why they have those dispositions and/or structural features which, in the good case at least, allow them to do so.[3]

There are at least two concepts of function at work in biology. The first applies to activities that traits in fact perform(ed). Consider cladistic systematics, the branch of biology that studies common descent and changes in phenotype as a function of descent. When studying a phenotypic trait, systematists ascribe a function to it either to mark continuity in the activity performed by that trait with that of traits in ancestral systems or as evidence of innovation in that trait or its activity (Griffiths 2006). For instance, a systematist might ascribe to the tail of *Crocodilus* the function of propelling the animal through its aquatic habitat in recognition of the fact that an ancestral genus, *Mystriosuchus*, made the same adaptive use of its archosaur tail (Griffiths 1994, 218–219). Or the systematist might ascribe to the carapace of *Proganochelys* (a genus of proto-turtle) the function of protection in recognition of its

[1] I use "activity" for both processes and continuous states, e.g., presence of the ventricular septum.

[2] I use "part" and "trait" interchangeably to cover system-level and subsystem traits, parts, components, phenotypes, characters, items, and genotypes except in contexts where using one of the other terms provides greater clarity.

[3] On the distinction between How-questions and Why-questions in biology and their relationship to functional analysis, see Mayr (1961); *cf.* Neander(2017b, especially Chapter 3)

novelty as a trait. In this case, functions are activities that traits perform(ed). Their ascription does not necessarily tell us what a trait should be doing, only what it does or did or its past or present causal role (Cummins 1975; Amundson and Lauder 1994; *cf.* Neander 2002; Garson 2016, 7, 50–51, 90–91).

The second function concept at work in biology is often discussed under the heading of "normal function." Normal functions are activities that traits are *supposed* to perform. Consider physiology, the branch of biology which is said to study the normal functions of parts of organisms (Roux 2014). When physiologists say of the heart that its function is to pump blood, they do so in full awareness that not all hearts pump blood. In this case, the functions referred to as normal are normative in the minimal sense that they *embody a standard for trait-activity* (Roux 2014, 2248; Garson 2016, 5–6, 36, 48). Ascribing a normal function tells us not what a token trait actually does but what that trait, *as a token of a particular type*, is supposed to do and, *thereby*, what it is supposed to be disposed to do and/or the structure it is supposed to have so that it can perform its function.[4] Identifying a standard for trait-activity and, thus, disposition and/or structure guides identification of instances of that trait *as being of the same type* despite variation between individuals, system types, and environments. A heart that cannot pump, is not disposed to pump, or fails to have the structure that allows it to pump is still recognizable as an instance of the type at least in part by appeal to its normal function. Ditto for morphologically distinct hearts across species and environments.

I do not take these two to exhaust the set of function concepts that are applied in biology. However, they are sufficient to point to a lack of uniformity in the application of a single function concept across the discipline. This lack of uniformity has driven several philosophers writing on the subject to adopt function pluralism (for instance, Godfrey-Smith 1993; Amundson and Lauder 1994; Allen and Bekoff 1995; Millikan 1999, 2002; Arp 2007; Bouchard 2013; Brandon 2013; Neander 2017a, b; Garson 2018; *cf.* Kitcher 1993; Steiner 2009; Nanay 2010; van Hateren 2017). Function pluralism is the view that no one account of function unifies application of the concept across biology. An effect of adopting pluralism is that disputes in the literature become territorial, characterized by arguments that some account explicates or fails to explicate the ascription of function within this or that (part of a) subdiscipline of biology (for an example of such a dispute, see Griffiths 1994; Amundson and Lauder 1994; Neander 2002; Rosenberg and Neander 2009).[5] The accounts at issue are labeled "descriptive." There are many descriptive accounts

[4] Note that some normal functions might not imply anything about the structure of the relevant part, say, if some behavioral or psychological functions are normal. However, because my focus is squarely within biology and because biological normal functions do imply normality in structure (see Neander 2002; Rosenberg and Neander 2009) I continue to mention normal structure in my description of normal function.

[5] A related debate in the literature is whether pluralism is best understood as being about *inter*disciplinary differences in application of the concept(s) or as being about *intra*disciplinary differences (see Garson 2018). The characterization in the main text of disputes in the literature is meant to be neutral on this debate concerning function pluralism. However, moving forward, I suppress relativizing to intradiscplinary differences. I also at times suppress relativizing to interdisciplinary differences, where doing so does not threaten clarity.

of function on the market. The "Assessing other accounts of normal function" section discusses only two, namely, the organizational account and the selected effects account. However, there is in addition the causal role account (e.g. Cummins 1975), the biostatistical account (e.g. Boorse 1977), various goal-contribution accounts (of which Boorse's is one) (e.g. Adams 1979), the propensity or life-chances account (e.g. Bigelow and Pargetter 1987), the weak etiological theory (Buller 1998), and the modal account (Nanay 2010).[6] As those familiar with the extant function literature will recognize, each of these accounts lays some claim to explicating a concept of function that is applied at least within some subdiscipline of biology.

I belabor the points about function pluralism as well as descriptive accounts of function and I restrict focus to the organizational and selected effects accounts for two related reasons. First, I argue that cancer biologists ascribe normal functions to parts of cancers (see "The ascription of normal functions to cancers" section). Second, I argue that the organizational and selected effects accounts fail to be descriptive of cancer biology in this respect despite the claim (albeit made in passing) that they are descriptive of this subdiscipline in just this respect (see the "Assessing other accounts of normal function" section). And, though I contend that my preferred account best describes normal function ascription in cancer biology, I too subscribe to function pluralism.[7]

In contrast to descriptive accounts, some accounts provide analyses of function that proponents claim biologists *should* take up and that stand to make their application of the concept uniform (most notably Millikan 1984, 1989, 1999, 2002). While I focus on descriptive accounts, proponents of prescriptive accounts should find this paper fruitful for what it reveals about cancer biology. Prescriptivists who claim that

[6] This list is not meant to be exhaustive.

[7] There are three further reasons that I do not consider Cummins (1975)'s or Boorse (1977)'s account. First, regarding the former, Cummins's account does not aim to explicate the ascription of normal function. As such, his account is only relevant if it turns out that I am wrong concerning the ascription of normal functions to parts of cancers in cancer biology (*cf.* Sect. 6.1). Second, regarding the latter, Boorse's account defines normal function with a view to giving an account of a negative conception of health, that is, health as the *absence* of disease. As such, he is explicit that the activities or processes that promote pathologies are contrary to those that promote or sustain normal function (Boorse 1977, 567). Since cancers are pathologies, they cannot have normal functions on Boorse's account by definition. Indeed, Boorse consistently assumes that cancer is an internal state of the organism which reduces normal functional efficiency or ability of some part(s) below some relevant threshold set by what is typical of the species—that is, he assumes that cancer is a disease (1976a, 66; 1977, 544, 547, 550, 560, 563; 1977, 47, 59– 60, 96, 63 fn.46; 2014,712). Moreover, he is explicit that cancers are non-functional down to the sub-cellular level (Boorse 2002, 65 fn.49, 85-86 fn.63). Indeed, Boorse goes so far as to claim that we can apply the biostatistical account in explicating the concept of disease in order to adjudicate cases of pathologists' or researchers' atypical usage (2002,53 fn.39). And I suspect he would find cancer biologists' ascription of functions to parts of cancers atypical in the relevant sense. That said, see Hausman (2012,521–522,534) for the claim that the notion of functional efficiency is applicable to parts of cancers. Third and finally, I argue elsewhere that difficulties type-individuating systems by appeal to reference-class are especially acute in the case of cancers due to their rank heterogeneity (Goldwasser accepted). Thanks to an anonymous reviewer for pushing me to clarify these points and to mention some additional descriptive accounts of function.

cancer biologists should not ascribe normal functions to parts of cancers need to provide an argument why cancer biologists should not be searching for standards applicable to part-activity across a given type of cancer.[8] I argue in the "Objections: loose talk and going wrong" section that they do in fact search for those standards with the aim of inducing failure in part-activity, disposition, and/or structure as part of targeted treatment. And I argue that this practice is substantiated by efficiently homing in on mechanisms that make for promising targets of intervention.

Desiderata: class adequacy and methodological adequacy

Returning to descriptive accounts of function, there are at least two ways that they can fail. First, they can be either too narrow or too broad with respect to the types of systems they consider.[9] An account is too narrow relative to a given subdiscipline of biology if it excludes systems of a type from having a type of function and biologists in that subdiscipline ascribe that type of function to parts of systems of the relevant type. For instance, say ecologists ascribe functions of a certain type to parts of ecosystems. If so, then any account of function that excludes ecosystems from having that type of function fails to be descriptive of ecology by being too narrow. By contrast, an account is too broad relative to a given subdiscipline of biology if it allows systems of a type to have a type of function and biologists in that subdiscipline knowingly decline to ascribe that type of function to parts of systems of the relevant type. For instance, say astrobiologists nowhere ascribe normal functions to parts of planetary systems—despite having ample opportunity to do so—because they think that those systems are just not such that their parts can embody a standard for part-activity. From the point of view of astrobiology, planets, asteroids, comets, circumstellar disks, etc. are just not the sorts of things that are *supposed* to perform certain activities or have certain dispositions or structural features rather than others. If so, then any account that allows for the ascription of normal functions to parts of planetary systems fails to be descriptive of astrobiology by being too broad. Avoiding both of these pitfalls constitutes a desideratum on descriptive accounts to be extensionally adequate concerning the types of system to which a subdiscipline of biology ascribes a type of function—I call this "class adequacy."

[8] Strictly speaking, this paper does not establish whether this claim or claims made in the "Objections: loose talk and going wrong" section (or in "The selected effects account" section) apply to Ruth Millikan's etiological, prescriptive account of *proper* function. Her technical notion of Normality is not restricted to the normality of normal functions ascribed in physiology and discussed in cancer biology nor obviously reducible to the normalizing force of evolution by natural selection. For instance, establishing what she calls a "reproductive family," to which proper functions are ultimately ascribed, can be done socially. A separate analysis is needed to discuss whether and how Millikan's view could deal with the ascription of normal functions to parts of cancers. I want to thank Colin Allen for pushing me to clarify this point.

[9] For an argument to this effect against Wright (1973)'s account of function, see Boorse (1976b). One can apply this strategy on the basis of the types of parts an account allows to have a type of function or the types of activities an account allows to count as a function. Regarding the former, an account that has it that, say, hearts do not have normal functions and aims to be descriptive inherits the burden of arguing that physiology does not ascribe normal functions to hearts. For an example of such an argument favoring Cummins's account, see Amundson and Lauder (1994).

A second way that descriptive accounts of function can fail is by providing conditions for the ascription of a type of function that are inconsistent with how biologists in a given subdiscipline actually go about ascribing those functions.[10] For instance, say that systematists neither explicitly nor implicitly appeal to natural selection nor need to when ascribing functions. If so, then any account of function that entails that ascription commits the ascriber to appealing to natural selection fails to be descriptive of cladistic systematics by being inconsistent with how functions are actually ascribed within that subdiscipline. Avoiding this type of criticism constitutes a second desideratum on descriptive accounts to remain consistent with methodology regarding ascription—I call this "methodological adequacy." An account that is consistent with how a type of function is ascribed in a given subdiscipline of biology stands a chance of being descriptive relative to that subdiscipline. Even better is when an account provides conditions for function ascription that biologists in the relevant subdiscipline *actually* apply. However, only bare consistency is necessary to satisfy methodological adequacy relative to a given subdiscipline.

Class adequacy and methodological adequacy together set a basic hurdle for descriptive accounts of function. Success both in identifying the class of systems whose parts are ascribed a type of function in a given subdiscipline of biology and in remaining consistent with how those functions are ascribed in that subdiscipline might not be sufficient to prove the soundness of a descriptive account. But they are necessary. When an account of function satisfies both desiderata relative to a subdiscipline of biology, I say that it is descriptive of the ascription of a type of function relative to that subdiscipline.[11] In the "Assessing other accounts of normal function" section, I test accounts of normal function against these desiderata with respect to the ascription of normal functions to parts of cancers in cancer biology (see also Goldwasser accepted). For now, I turn to a representative example of such ascription.

The ascription of normal functions to cancers

A consistent challenge for cancer biologists is dealing with treatment relevant variation among cancers. Here is a non-exhaustive list of clinically significant dimensions along which individual cancers can differ: anatomical site and tissue type of origin, genome, mutation rate, growth rate, tumor formation, incidence and rate of metastasis, the cancer microenvironment, and initiating agent. Like inquiry in any domain, a central task in cancer biology is finding within all of this variation sameness that is of causal and explanatory relevance. For instance, cancers have historically been

[10] For illustrative examples of arguments to this effect against Neander's selected effects account, see Amundson and Lauder (1994); Griffiths (2006,16-18).

[11] However, as I focus on the ascription of normal function, I often suppress relativizing to function-type when claiming that an account is or fails to be descriptive. And since I focus almost entirely on one type of case, namely, that in which cancer biologists ascribe normal functions to parts of cancers, I suppress relativizing to system-type and/or to intradisciplinary boundaries when claiming than an account is or fails to be descriptive.

classified by anatomical site, tissue type, stage, and grade (Plutynski 2018,especially Chapter 1 and the Appendix). A stage I, grade 1 lung adenocarcinoma is a cancer originating in glands (tissue) in the lung (site) that has yet to form a tumor (stage) and whose cells still resemble healthy, somatic cells (grade).

This standard classificatory scheme is effective at grouping cancers together and bears explanatory fruit. For instance, other properties relevant to treatment often cluster around tissue type, stage, and grade. Only some types of tissue form solid tumors, i.e., clumps of cancer-associated cells. Size is a property of solid tumors that is partially indicative of stage and is predictive of disease progression. And the degree of apparent similarity between cancer cells and healthy cells is predictive of growth rate and metastatic potential—grade 4 cancers with cells very unlike their healthy kin are likely to grow and metastasize more quickly and aggressively.

However, the standard scheme is not perfect (Plutynski 2018, 2019). For instance, cancers originating in the same organ can be more similar genetically to those originating in a different organ than to each other. Precision oncology depends on targeting particular mutated genes and proteins. So, sameness in anatomical site of origin is not always explanatory or helpful for treatment. Luckily, the standard scheme represents only one of many tools for finding treatment relevant sameness among cancers.

One tool that cancer research shares with much of biology is the use of models. Following Godfrey-Smith (2006, 2009b) and Levy (2015), I assume a broad notion of "model" on which models are representations that abstract and idealize features of what they represent—their targets—with a view to predicting or explaining the behavior of those targets (*cf.* Weisberg 2007). Models may be concrete, comprising a physical analogue of the target(s), or abstract, comprising a representation the vehicle of which is not supposed to be analogous to the target(s). Models may represent targets directly, say, by containing the part whose activity in the target is of interest or indirectly, say, by having the value of a variable go proxy for some quantifiable property of the target, for instance, the size of a target population. Models predict or explain the behavior of their targets in much the way maps represent a territory—by resembling or being similar to those targets in ways relevant to a particular explanandum of interest (Thomson-Jones 2005; Elgin 2017; Potochnik 2017).[12] Often in cancer biology, the models used are concrete and may represent their targets directly or indirectly (however, for an example of an especially influential *abstract* model of cancer progression, see Armitage and Doll 1954). These models are often populations of human or mouse cells with particular genomes that reliably produce tumor phenotypes of interest. Cancerous model cell-lines are injected into mice or zebrafish to see how well they progress *in vivo* or are grown into tumors in Petri dishes *in vitro*. As we will see immediately below and in the "Applying MA to peinado and colleagues' ascription" section, the use of models in cancer biology is integral to discovering part-activities that embody a standard for contributing to system-level activities of interest.

[12] Following Ronald N. Giere (1999, 2004) and Godfrey-Smith (2006, 2009b), I remain neutral on the exact resemblance or similarity relation that obtains between model and target.

Case study: the normal function of melanoma-derived sEV

A second, related tool cancer research shares with much of biology is the ascription of normal functions, or so I now argue by example. A widely cited paper, Peinado et al. (2012), claims to have "explored *the function* of melanoma-derived exosomes in the formation of primary tumors and metastases" (883; my emphasis). And Zhang and Yu (2019), reporting their results, say "[Peinado et al. (2012)] have advanced our understanding of *the novel function* of exosomes in pre-metastatic niches" (458; my emphasis). The (novel) function explored and of which our understanding is advanced is the delivery of a protein to cells in bone marrow via membrane-bound packages produced mostly by late-stage melanomas (Figure 1). Through a series of experiments using cell-line and mouse models, Peinado and colleagues identify a standard for the activity of small extracellular vesicles (sEV) or "exosomes" and whose performance results in greater primary tumor growth and more aggressive metastasis. Specifically, melanomas produce sEV carrying mesenchymal-epithelial transition factor (Met), an oncoprotein that can trigger several signaling pathways in cells (Organ and Tsao 2011). Melanoma-derived sEV carrying Met travel through the blood to cells deep in bone marrow which have yet to differentiate. Receiving Met sets off a cascade of signaling in those progenitor cells that mobilize them to inflame distant organs, exhibit vascular leakiness in the tissues they migrate to, and produce vascular tissue. The result is pre-metastatic niche formation, which facilitates greater primary tumor growth and metastasis (Quail and Joyce 2013; Mashouri et al. 2019; Gonzalez et al. 2020).

Peinado et al. (2012) features the ascription of a normal function. Beyond use of the definite article, both Peinado and colleagues' and Zhang and Yu's talk of the (novel) function of melanoma-derived sEV generalizes over them without distinguishing between later stages of melanoma, sEV that successfully deliver Met, sEV that are deformed or fail to carry Met, or melanomas that fail to produce any sEV at all. Generalizing over these divergences, effectively type-individuating melanoma-derived sEV in the process, is no accident (see also Zebrowska et al. 2020). In particular, generalizing afforded experimenters the opportunity and ability to identify a standard applicable to melanoma-derived sEV activity in relation to its contribution to pre-metastatic niche formation.

Let me explain. In the process of identifying the function, Peinado and colleagues examined sEV production and Met delivery across early- and late-stage melanoma patients as well as low and highly metastatic melanoma mouse models. They also examined sEV production in melanoma mouse models designed to produce sEV lacking Met, fewer sEV, or no sEV. The point was to home in on the mechanism(s) responsible for sEV mediated pre-metastatic niche formation. This in turn required the experimenters to re-identify sEV or mark their absence and to identify and relate in a systematic way the effects of their presence or absence on niche formation. Some of this was accomplished by tracking sEV-related proteins in blood. However, at least some of it was accomplished by hypothesizing the activity melanoma-derived sEV are *supposed* to perform for the cancer, positing the dispositions and/or structural features that in the good case (for the cancer) allow them to perform that activity. The hypothesis drew

the experimenters to look for sEV in bone marrow and potential sites of metastasis in patients and mouse models. It also drew them to infer from a lack of sEV, reduced tumor growth, and reduced metastasis that they had successfully disrupted the functional dispositions and/or structural features of melanoma-derived sEV in models designed to produce sEV lacking Met, fewer sEV, or no sEV.

In confirming their hypothesis via intervention on cell-line and mouse models, Peinado and colleagues show that deformed sEV and sEV that do not carry Met are, in some minimal sense, *supposed* to deliver Met to bone marrow and are thus in some minimal sense *supposed* to have the dispositions and/or structural features that allow them to do so. I discuss in just what sense they are supposed to have these dispositions and/or structural features in the "Applying MA to peinado and colleagues' ascription" section. For now, what is important is that the generalization over both defective and non-defective sEV in the process of discovering their function and sites of possible clinical intervention suggests that the ascription identifies a standard for the activity of that part in relation to the system-level activity of interest. In which case, delivering Met to bone marrow is a normal function of melanoma-derived sEV.

Assuming Peinado et al. (2012) is representative of the ascription of normal functions in cancer biology, such ascription informs the desiderata introduced in the "Desiderata: class adequacy and methodological adequacy" section. Recall that class adequacy states that a descriptive account should be neither too narrow nor too broad regarding the type of system to which the relevant subdiscipline of biology ascribes a type of function. If cancer biologists ascribe normal functions to parts of cancers then class adequacy dictates that an account is descriptive of cancer biology only if it allows (parts of) cancers to have normal functions. Recall that methodological adequacy states that a descriptive account should not set out conditions for the ascription of a type of function that are inconsistent with how biologists within the relevant subdiscipline actually go about ascribing that type of function. Peinado and colleagues employed several methods en route to ascribing melanoma-derived sEV their normal function. However, as I argue in the "Applying MA to peinado and colleagues' ascription" section, the use of cell-line and mouse models was essential. If that is right and cancer biologists regularly employ models to identify normal functions of parts of cancer then methodological adequacy dictates that an account is descriptive of cancer biology only if it is consistent with the role modeling plays in ascribing normal function to parts of cancers. We now have two necessary conditions on accounts of function that aim to be descriptive of cancer biology. Such accounts are descriptive of cancer biology only if they allow for the ascription of normal functions to (parts of) cancers and only if they are consistent with the use of models in discovering those functions. In the "Assessing other accounts of normal function" section, I assess accounts on whether they satisfy both conditions. In the "Objections: loose talk and going wrong" section, I consider and reject two objections to the claim that cancer biologists ascribe normal functions to parts of cancers. I now turn to introducing and applying the Modeling Account of Normal Function.

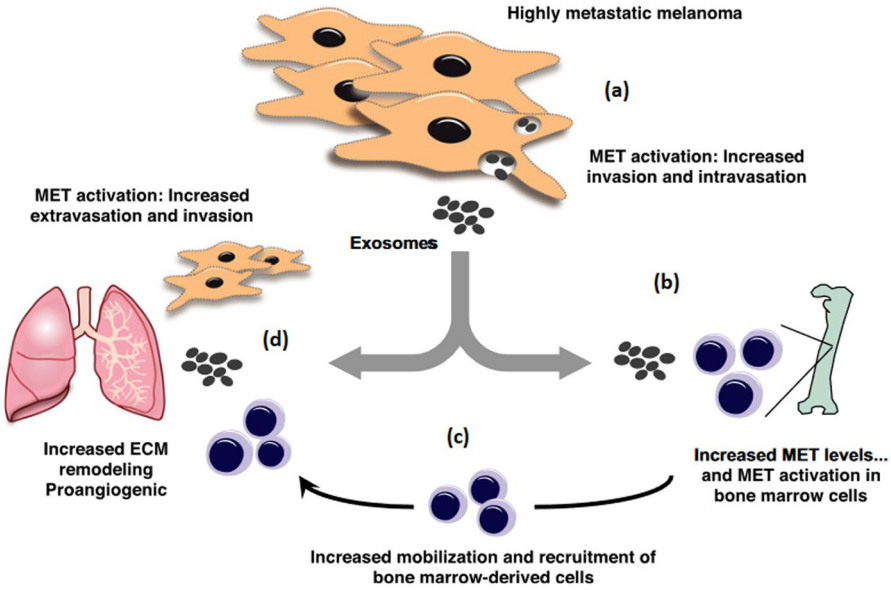

Fig. 1 **a** Melanoma-derived small extracellular vesicles (sEV) (here labeled "exosomes") carry mesenchymal-epithelial transition factor (Met) (here labeled "MET") to bone marrow progenitor cells **b** as well as to sites of metastasis (here represented by the lungs) **d**. The function ascribed to melanoma-derived sEV in Peinado et al. (2012) is the delivery of Met to bone marrow progenitor cells **b**, which mobilizes those cells **c** to inflame sites of metastasis, induce vascular leakiness (here labeled "extravasation"), and promote vascular growth (here labeled "proangiogenic") altogether facilitating tumor growth and metastasis (here labeled "invasion") **d**. Adapted from Matsumoto et al. (2017)

The modeling account of normal function

Introducing the account

The Modeling Account of Normal Function (MA) is a member of a family often discussed under the heading of "organizational accounts" (for instance, Schlosser 1998; McLaughlin 2000; Mossio et al. 2009; see also Garson 2017a). Such accounts hold that the class of systems to which functions are ascribed in (much of) biology have the following two distinguishing features. First, they are organized in the sense that they are arranged into, in principle, distinct activity-based units at multiple levels. The cardiovascular system can be distinguished from other organ systems by the former's transporting nutrients and waste to and from tissues; the heart can be distinguished from arteries and veins by pumping; the aortic valve can be distinguished from the ventricular septum by facilitating certain fluid dynamics between the left ventricle and the aorta, and so on. Second, these systems are self-maintaining in the sense that the activity of their parts is what produces, reproduces, and maintains the arrangement of parts and activities that constitute them. The heart's pumping blood is part of a process of nutrient and oxygen distribution which has as effects the production, reproduction, and

maintenance of blood and heart tissue. These in turn set up the conditions for further pumping and are part of what leads to new organisms with new hearts.

I call these "organized self-maintaining systems." Consider as a contrast to these systems a lit candle. A lit candle can be distinguished into wick, fuel, and flame. However, it cannot be decomposed into distinct, activity-based units at multiple levels: there is only the single activity of consumption of fuel by flame. Moreover, lit candles are not self-maintaining: consumption is not produced except by something else lighting the wick and does not itself produce, reproduce, or maintain the fuel. Thus, unlike, say, vertebrates, a lit candle is not an organized self-maintaining system.

MA differs from other organizational accounts, in particular the account originally put forward by Mossio et al. (2009), by claiming that the ascription of *normal* function is part of a practice of modeling system-level activities constitutive of self-maintenance relative to the type of system under investigation. MA proposes the following condition: if a part-activity is a normal function then there is a class of models of the relevant system-level activity whose members are improved by including a representation of that part and its activity. According to MA, biologists ascribe normal functions when they identify that the disposition(s) and/or structural feature(s) of the function-bearing part are of causal relevance to an effect which, in turn, forms part of an explanation of how organized systems of the type maintain themselves (Mossio et al. 2009; Lennox 2010). The cause of that effect is the part-activity the relevant type of part standardly performs and the effect is the contribution that activity makes to a system-level activity of interest (which system-level activity at least partly constitutes self-maintenance). Biologists are motivated to make these ascriptions by an interest in understanding how biological systems of a type work, where this means how they effectively maintain themselves within highly constrained types of organization. Importantly, system type is not to be understood in terms of species or other genera used to characterize *organisms*. MA is meant to apply to biological systems while remaining neutral on whether those systems constitute individual organisms. Cancers are a case in point.[13]

[13] One might object that a cancer cell's or tumor's satisfying conditions on counting as an organized self-maintaining system suffices for their counting as organisms. In which case, there is no need to remain neutral on whether cancer cells or tumors are individual organisms. In response, some putatively organized self-maintaining *biological* systems are not obviously organisms. For instance, ecosystems are biological systems comprised of multiple levels of in principle distinct, activity-based units whose activities produce, reproduce, and maintain the arrangements and parts of those systems. Yet, it is not obvious (and, thus, would require independent argument in favor of the claim) that an ecosystem is a so-called "superorganism" rather than a distinct kind of biological individual worth studying in its own right (see van Baalen and Huneman 2014). Analogously, without independent reason for thinking of cancer cells or tumors as individuals, their being organized self-maintaining systems is insufficient to classify them as organisms. What makes cancers like ecosystems in this context is vagueness around what counts as an individual. This vagueness is introduced by cancers being atavistic, effectively returning to a state in evolution between total unicellular anarchy and heavily enforced multi-cellular cooperation (Okasha 2021). The breakdown in the integrity and coherence of intraorganismal interactions exacerbates the vagueness around what counts as an individual organism: a cancer cell could be an organism, part of a tumor, or a diseased part of its host. A tumor could likewise be an organism, an "ecoysystem" of cancerous individuals and cancer-related entities, or a diseased part of its host. Fortunately, a merit of organizational accounts in general and MA in particular is that there is no requirement on these accounts to decide whether cancer cells or tumors are organisms so long as it is granted that they are organized self-maintaining systems. Thanks to an anonymous reviewer for pushing me to clarify this point.

Here is a more precise definition of MA, where φ stands for a type of part-activity, p an individual part, S an individual system, A a type of system-level activity, M_{SA} a class of models indexed to systems of S's type and their A-ing, and $R_{p\varphi}$ a representation indexed to p and its φ-ing:

(MA) An activity, φ, of a part, p, of a biological system, S, of a given type is a normal function if and only if:
C1. the presence of parts of p's type among systems of S's type is an effect of the contribution ps make by tokening φ to the self-maintenance of Ss; and
C2. there is a class of models, M_{SA}, such that, for any two models in that class, m_{SA}, m'_{SA}, were m_{SA} to include a representation of p and its φ-ing, $R_{p\varphi}$, and were m'_{SA} not to include $R_{p\varphi}$ then m_{SA} would better predict or explain how systems of type S maintain themselves by tokening A than m'_{SA}.

(C1) is a metaphysical condition. It states that a normal function is a 4-place predicate relating activity-type, part, system, and contribution to system self-maintenance (*cf.* Weber 2017). In particular, (C1) states that a requirement on a part's having a normal function is that the part (or parts of the same type) is maintained, produced, or reproduced in the system (or systems of the same type) as an effect of the activity of that (type of) part. This is just what we should expect of the functional parts of organized self-maintaining systems. Again, the contribution to vertebrate self-maintenance made by the heart's pumping sets up the conditions for further pumping and is part of what leads to new vertebrates with new hearts. (C2) is a counterfactual epistemic condition. It states that there is a class of models whose members benefit from representing function-bearing parts and their activities, namely, those which predict or explain system-level activities which are (partly) constitutive of self-maintenance and for which the relevant function-bearing parts, per (C1), are specific difference-makers.[14] Finally, as I am non-committal regarding the resemblance or similarity relation that obtains between model and target (fn.12), I am correspondingly liberal regarding representation. $R_{p\varphi}$ can be a variable in a mathematical or causal model, a physical analogue of a part of the target, or anything in between.

Before moving on, I want to clarify (C2). It is not that the model which best predicts performance of some system-level activity or best explains how a system maintains itself via the performance of that activity is in every case a model that includes representations of every part with a normal function. (C2) does not quantify over all models of the relevant-system level activity in order to allow for cases in which such a model excludes representations of parts when including them would worsen the model. For instance, Setty et al. (2008) provide a model of the organogenesis of the pancreas in mice which fails to represent adhesion proteins between the cells that

[14] On causation as difference-making see Woodward (2003); Halpern and Pearl (2005); Joseph and Judea (2005); Sartorio (2005); Loew (2019) and as applied to explanation in biology, see Woodward (2010). Following the latter, part of what I am claiming is that models that represent parts with normal functions as well as those functional activities are modeling specific causes of the relevant system-level activities. Thanks to an anonymous reviewer and Andrew Rubner for pushing me to clarify this point as well as the formulation of (C2).

form the bud and eventually the organ. Because there are several such proteins and their functional activity is thereby made redundant, no representation of any particular adhesion protein is needed. In fact, Setty and colleagues' models represent the cells as held together but do not represent any such protein. Including a representation of some adhesion protein might well have impeded the model by including unnecessary detail in accounting for the underlying mechanisms of pancreas development in mice. (C2) can allow for this kind of case, since it tells us that, for every part that has a normal function, there is a class of models whose members benefit from including a representation of that part and its activity. In particular, the class of models is that of the relevant system-level activity for which the relevant part-activity is a difference-maker.

Before applying MA to the example of melanoma-derived sEV introduced in "The ascription of normal functions to cancers" section, I want to consider an example that is more germane to the function literature. The heart is ascribed its normal function when certain of its dispositions or structural features are identified as causally relevant to the transportation of nutrients and waste in vertebrates. Nutrient and waste transportation is an essential part of how vertebrate systems as a type achieve self-maintenance. This is the case for vertebrates whose hearts cannot pump blood too—they do not maintain themselves for very long after all. If this is right then there is a class of models of nutrient and waste transportation in the vertebrate circulatory system that should allow us to predict or explain the success or failure of that transportation in individual vertebrates in part by observing whether or how their hearts measure up in comparison to those models. And we should be able to identify divergences in the dispositions or structural features of individual vertebrate hearts as such by appeal to those models. Models of vertebrate circulatory systems within the relevant class that include an abstracted or idealized representation of the vertebrate heart are preferable with respect to accomplishing these predictive and explanatory tasks. Unsurprisingly, models of vertebrate circulatory systems in physiology and comparative anatomy in fact include such representations.

Importantly, how MA distinguishes normal functions and accounts for model-based explanations of the organization (or lack thereof) and self-maintenance (or lack thereof) of individual biological systems has the result that normal function is primarily an epistemic or explanatory notion rather than a metaphysical kind that picks out a category of activity. There might be no one thing or cluster of properties that picks out the normal functions from among all of the types of part-activities that are of interest to biology. Skepticism towards the metaphysical unity of normal functions places MA within a pragmatist tradition in philosophy of science and philosophy of biology in particular, according to which at least some scientific categories, rather than tracking unified kinds, group otherwise heterogeneous natural phenomena in a way conducive to scientific inquiry (Cummins 1975; Hardcastle 2002). This is not to say that some normal functions are not generally distinct in kind from some non-normal functions. However, as I show in the "Assessing other accounts of normal function" section, accounts that hold that, in the first instance, normal functions constitute a metaphysical kind struggle to handle cases like Peinado and colleagues' ascription. It is to applying MA to this ascription that I now turn.

Applying MA to peinado and colleagues' ascription

Before seeing whether the example provided by Peinado et al. (2012) meets (C1) and (C2) of MA, I want to state explicitly that cancers are organized self-maintaining systems. They can be decomposed into activity-based units at multiple levels. Cancer associated fibroblasts can be distinguished from cancer cells by the support and protection the former provide the latter; sEV can be distinguished from cell nuclei by the former's disposing waste and carrying signaling proteins; Met can be distinguished from γ-actin-1 by the former's sitting on the plasma membrane of cells and catalyzing signaling processes; etc. And the activities of these parts at both the cellular and tumor level produce, reproduce, and maintain the arrangement of parts which constitutes the cancer (at least until patient death).

Let us apply MA to the example provided by Peinado et al. (2012). Delivering Met to bone marrow is a normal function of melanoma-derived sEV if and only if the following holds. First, (C1) the presence of melanoma-derived sEV among melanomas is an effect of pre-metastatic niche formation mediated by sEV Met delivery. Second, (C2) there is a class of models of melanoma pre-metastatic niche formation such that, for any two models within that class, were one model to include a representation of melanoma-derived sEV and their efficacious delivery of Met to bone marrow and were another model from the same class not to then the former model would better predict or explain pre-metastatic niche formation.

Starting with (C1), recall that Peinado and colleagues' ascription suggests that, in some minimal sense, melanoma-derived sEV are *supposed* to deliver Met to bone marrow. MA holds that they are supposed to do so in the sense that they make a contribution to melanoma self-maintenance—specifically to pre-metastatic niche formation—by delivering Met to bone marrow and that this results in their continued presence among melanomas. Consequently, we should expect there to be a correlation between the prevalence of sEV carrying Met and the persistence and propagation of individual melanomas. We can see this by looking more closely at the experiments that Peinado and colleagues carried out. Consider Table 1. The first three rows describe experiments showing that patients with late-stage metastatic melanoma and highly metastatic melanoma mouse models exhibit high concentrations of circulating sEV and sEV-related proteins compared to patients with stage I or stage II melanoma. These experiments suggest that melanoma-derived sEV perform a certain activity that has as effects disease progression and, in turn, their continued presence among melanomas.

As Met delivery is hypothesized to contribute to melanoma self-maintenance, MA predicts a correlation between a lack of sEV carrying Met and a drop in efficacious propagation and persistence of melanoma. It holds that the part of melanoma self-maintenance constituted by pre-metastatic niche formation depends, at least in part, on the dispositions and/or structural features of melanoma-derived sEV that allow them to deliver Met. And it is in this sense that melanoma-derived sEV are supposed to have those dispositions and/or structural features. Consider the last two rows of Table 1. They describe experiments showing that reducing Met production and sEV production each result in smaller primary tumors and fewer metastases compared to highly metastatic mouse model and

Table 1 Experiments in Peinado et al. (2012); mouse model cell-lines are in bold, human model cell-lines are in regular typeface

Design	Model cell-line	Results
Isolate melanoma-derived sEV plasma of human subjects.	N/A	High concentrations of sEV related protein (CD63, CD9, MHC-I) in late-stage melanoma patients with poor prognosis and highly metastatic mouse model.
Test for sEV related melanoma diagnostic signature using mass spectrometry and retrospective analysis.	**B16-F10**, **BF16-F1**, SK-Mel-28, SK-Mel-202, SK-Mel-265, SK-Mel-35, **LLC**	High concentrations of melanoma-specific protein (TYPR2) as well as proteins associated with oncogenesis (HSP90), cell maintenance under stress (HSC70), and inflammation (VLA-4) among late-stage melanoma patients compared to controls. TYRP2 discovered as diagnostic of progression past stage III.
Analyze distribution of sEV, gene expression, and metastatic burden in tissue of naive mice injected with sEV=, first, one time over a 24 hour and 48-hour period and then 3 times a week over a period of 19, 24, and 28 days.	**B16-F10**, **BF16-F1**, **melan-a**, SK-Mel-28, SK-Mel-202, **LLC**, MCF-7, SW480, SW620	Significantly greater distribution of sEV and gene expression for inflammation and extracellular matrix remodeling protein (S100A8, S100A9). When also injected with tumor cells, significantly greater metastatic burden in lungs and bone marrow for highly metastatic melanoma and mouse model.
Transplant bone marrow previously exposed to B16-F10 sEV or B16-F1 sEV for 28 days into lethally irradiated mice.	**B16-F10**, **BF16-F1**	Increased metastases in typical and atypical locations, increased primary tumor and metastatic growth, increased vasculogenic and hematopoietic bone marrow derived cells (BMDC) in mice with B16-F10 educated bone marrow.
Test Met expression in B16-F10 sEV and sEV derived from Met-knockdown-B16-Fl0 tumor cells. Test for downstream mediators in BMDC. Compared results to late-stage melanoma patients.	**B16-F10**, **BF16-F1**	Significant increase in Met in untampered B16-F10 sEV. Significant increase in Met and vasculogenic and hematopoietic BMDC and mice injected with untampered B16-F10 sEV and tumor cells. Corroborated with high levels of Met and vasculogenic and hematopoietic BMDC in late-stage melanoma patients.
Test metastatic burden and mobilized BMDC in mice injected with B16-F10 sEV vs. Rab27a-knockdown-B16-F10 tumor cells. Inject Rab27a-knockdown-B16-F10 sEV into mouse model.	**B16-F10**, SK-Mel-28	Increased metastatic burden and mobilized BMDC in mice injected with untampered B16-F10 sEV. Similar increases when injected directly with B16-F10 sEV from Rab27a-knockdown-B16-F10 tumor cells despite knockdown.

late-stage patients. These experiments suggest that pre-metastatic niche formation depends on Met delivery by melanoma-derived sEV. Taken together, Peinado and colleagues' experiments suggest that the presence of melanoma-derived sEV among melanomas is an effect of pre-metastatic niche formation mediated by sEV Met delivery. Therefore, (C1) of MA applies.

Moving on to (C2), representations of sEV and Met delivery were integral to modeling pre-metastatic niche formation. We see this, again, by looking to Table 1. The experiments described in the first three rows feature the use of cell-line and mouse models to identify mechanisms of pre-metastatic niche formation. Peinado and colleagues constructed models of melanoma as well as of lung, breast, and colon cancers with varying degrees of metastatic potential. The experiment described in the fourth row features the use of models to home in on the intermediate effect of interest, namely, bone marrow mobilization. In this case, the experimenters transplanted bone marrow that had previously received sEV derived from highly metastatic melanomas into mice. The experiments described in the last two rows feature the use of models to specify and confirm the activity melanoma-derived sEV perform. Experimenters reduced the production of Met or sEV in cell-line and mouse models, resulting in reduced bone marrow mobilization and, in turn, a reduction in pre-metastatic niche formation. Every link in the inferential chain to the function ascription was forged by the construction and use of models. Importantly, the predictive and explanatory power of the models increased with the inclusion of a representation of sEV carrying Met and Met delivery. Had they not included that representation, albeit in the form of those very sEV, Table 1 shows that there is some model which would have predicted or explained as much or more about how the pre-metastatic niche is formed during disease progression by including such a representation. Therefore, (C2) of MA applies.

MA applies to the example provided by Peinado et al. (2012). I claimed in the previous section that the example is representative of normal function ascription in cancer biology. If this is right then MA satisfies both class adequacy and methodological adequacy at least relative to cancer biology. MA satisfies class adequacy by avoiding restricting scope too much, for instance, to organisms or widening it too much, for instance, to lit candles. And it satisfies methodological adequacy by explicitly assigning a role to modeling in ascribing normal functions in cancer biology. We thus have reason to believe that MA is descriptive of at least cancer biology. In what follows, I consider how other accounts of function—accounts which hold that normal functions are metaphysically distinct from other kinds of activity—fare with respect to satisfying class adequacy and methodological adequacy relative to cancer biology.

Assessing other accounts of normal function

In this section, I critically assess two other accounts in contrast to MA: the organizational and selected effects accounts. Some of their proponents and critics have suggested in passing that one or both explicate the ascription of normal functions in cancer biology (for instance, see Garson 2017a,1100). In assessing whether these accounts meet both

class adequacy and methodological adequacy relative to cancer biology, I uncover some difficulties each faces. I offer ecumenical readings on which modified versions might account for the ascription of at least some normal functions to cancers in cancer biology.

The organizational account

I start with the account initially put forward by Mossio et al. (2009), as it is the closest relative of MA and the most thoroughly developed and extended organizational account (*cf.* Schlosser 1998; McLaughlin 2000). According to Mossio and colleagues' organizational account (OA), a token trait, p, has a function, φ, within the organization, O, of a token system, S, if and only if:

O1. p exerts a constraint that contributes to the maintenance of O in S;
O2. p is maintained under some constraints exerted by O;
O3. S realizes organizational closure.[15]

Like MA, the organizational account holds that the systems to which functions are ascribed in (much of) biology are organized self-maintaining systems. Recall that biological systems are organized in the sense that they can, in principle, be decomposed into activity-based units at multiple levels.[16] On OA, the organization of a system is the arrangement of traits and the coordination of the constraints that they exert. Constraints are influences that traits exert on ongoing processes. The influence of a constraint is asymmetric: the ongoing process is altered by the trait while the trait is unaltered by the process and the trait cannot directly influence itself by exerting its constraint(s). For instance, the heart exerts a constraint on blood flow by pumping. Pumping alters blood flow while preserving the heart. And the heart only influences itself indirectly, through the mediation of other traits exerting their constraints. A system realizes organizational closure when its traits mutually constrain each other, resulting in the maintenance of a particular organization among those traits. As Mossio et al (2009,824-825) put it, organizational closure is "a circular causal relation between some [higher-level] pattern or structure and [lower-level] dynamics and reactions" such that "a [lower-level] process is subject to closure in a self-maintaining system when [that process] contributes to the maintenance of some of the conditions required for its existence."[17] Finally, functions are relativized to individual systems and to the particular arrangement(s) of parts which allow those

[15] Taken from Saborido et al. (2016,267). Variables replaced for consistency.

[16] Mossio and colleagues call this "organizational differentiation" (2009,826).

[17] Montévil and Mossio (2015,186) give a formal definition of organizational closure in terms of mutually dependent constraints acting on the thermodynamic flow of matter and energy through a system. A constraint, C_i, is subject to closure just in case I) to exert its influence, C_i depends directly on the influence of at least one other constraint in the closed system, C_j, and II) there is at least one other constraint in the closed system, C_k, that depends on the influence exerted by C_i. C_i depends directly on C_j just in case no other causal process mediates the influence of C_j on C_i during the time course during which C_j exerts influence over C_i. Here is a more precise version of the example in the main text: systolic blood pressure within an appropriate range at some time depends directly on contraction of the heart's ventricles (at or immediately preceding that time) and several processes within the circulatory system depend on systolic blood pressure being within that range. Thus, systolic blood pressure within the appropriate range (at time t) is subject to closure. Thanks to an anonymous reviewer for pushing me to clarify this point.

systems to realize organizational closure at a given moment. Mossio and colleagues call the latter, *momentary* arrangements "regimes of self-maintenance."

MA is in agreement with OA both concerning the class of systems that are given functional explanations in (much of) biology and concerning the relationship between functional activity and system self-maintenance. Assuming cancers are organized self-maintaining systems, OA *appears* to satisfy class adequacy relative to cancer biology. However, OA is not, in the first instance, an account of normal function. To see this, consider the claim that my nose has the organizational function of holding up my glasses. Suppose one regime of my self-maintenance—one particular, momentary organization of me—is me wearing my glasses. Call this "me+glasses." (O1) My nose exerts a constraint, namely, holding my glasses up, that contributes to the maintenance of me+glasses by allowing my eyes to foveate. (O2) My nose is maintained under some constraints exerted by me+glasses, say, by me+glasses navigating the world without walking into walls or falling off of cliffs. Finally, (O3) I as me+glasses realize organizational closure at least whenever the regime of me+glasses depends on my nose exerting some constraint that thereby indirectly sets up the conditions for its exerting that very constraint. My nose's holding up my glasses contributes to the continued existence of me+glasses by allowing foveation and, thereby, indirectly sets up the conditions for my nose to hold up my glasses. So, my nose has the function of holding up my glasses on OA. However, it is not the *normal* function of my nose to hold up my glasses. Contributing to the maintenance of me+glasses by holding up my glasses is an incidental benefit of the structural features of that trait type. After all, a sufficiently low nasal bridge might fail to support my glasses (they do not have nose-pads) and, yet, be a fully functioning token of the type "nose." In which case, it is not a normal function of the nose to hold up glasses and, thus, as stated, the conditions of OA are not sufficient for normal function.[18]

In fact, Mossio et al. (2009, 830–834) anticipate this gap using this very example. They claim that one can recover normal functions through what they call "primary functions." More specifically, they claim that we can type-individuate systems by the set of regimes of self-maintenance that those systems must implement to remain viable or that require the least number of intervening part-activities to contribute to self-maintenance (Mossio et al. 2009, 829–832). A primary function of a trait is whatever activity or activities contribute(s) to the maintenance of regimes within that minimal set. So, the primary function of the heart is to pump blood because that is the constraint that it exerts which contributes to regimes within the minimal set characteristic of vertebrates. By contrast, even if the heart contributes to the maintenance of a human being by making a wooshing sound, its doing so is not its primary function, since pumping—which causes the sound—requires fewer intermediate activities to promote self-maintenance among the set of human beings. Mossio and colleagues claim that primary functions mostly overlap with normal functions. They also claim that the primary function of a trait is very likely what that

[18] Thanks to both anonymous reviewers for pushing me to clarify how me+glasses realizes closure on OA and why this is nonetheless insufficient for holding up my glasses to count as a normal function of my nose.

trait was selected to do by natural selection (see "The selected effects account" section below). In effect, OA claims that normal functions supervene on primary functions, where those primary functions are selected by natural selection.

Unfortunately, recovering normal function through primary function will not work for cancer. First, even if parts of cancers have primary functions, it is not clear that their normal functions are what they were selected to perform. Setting that aside for now, a further problem for OA is that primary functions are not necessary for normal function ascription in cancer biology. Consider the tumor protein p53 gene (Tp53). In healthy cells, this gene encodes a protein, p53, that functions as a tumor suppressor by preventing cells with damaged DNA from replicating or by inducing programmed cell-death. Mutation of this gene in cancers is common, occurring in over 50% of them, but not universal. Such mutation is not part of the minimal set of regimes of self-maintenance even within antecedently type-individuated cancers, for instance, breast cancer. Moreover, several cancers disrupt the production of p53 without exhibiting any mutated Tp53. Despite having no primary function on OA, several activities of mutated forms of Tp53 have been identified as standard across several types of cancer and as making contributions to those cancers' self-maintenance. Tp53 mutants have thus been ascribed normal functions (for an overview, see Chiang et al. 2021). The point generalizes: if cancers have something in common, it is that they are exceptionally heterogeneous both in their traits and in how they maintain themselves. This heterogeneity means that, on OA, most if not all parts of cancers fail to have primary functions and, thus, cannot have normal functions. Yet, normal functions are ascribed to parts of cancers. This constitutes a failure to satisfy class adequacy relative to cancer biology.

At this point, one might object that insisting that normal functions are (properly thought of as) picking out type-level activities of parts or whole systems is undue. Once this requirement is dropped, OA can effectively recover normal function and its role in modeling in cancer biology (and beyond). Indeed, as Saborido et al. (2016) put it, when accounting for the possibility of dysfunction:

> The organizational interpretation of "correct functional behavior" is very different from the concept of "normal function" [...] we [do not] need to appeal to [...] an "idealized type" [...] to justify when an organism is functioning incorrectly. The normativity of organizational [functions and] malfunctions is based on the organizational properties of each token living being (115).

As Saborido and colleagues make clear, they do not understand the relevant function concept to pick out standards of activity across types of system (or relative to types of part). Rather, correctness in functional behavior is determined within each individual organized self-maintaining system by the enforcement of a norm of a higher-order regulatory constraint onto one of its lower-order constraints.[19] What is more, one might point out that, building on Saborido et al. (2016); Bich et al. (2020) claim that we can develop models of "correct functional behavior" by attending to

[19] Saborido et al. (2016, 109–111) call such enforcement in the context of system viability "functional presupposition."

the interactions of higher-order regulatory constraints and their impact on the lower-order constraints they regulate. Bich and colleagues use glycemia regulation as an example and sketch a model of the interactions of multiple higher-order constraints which regulate glucose uptake, food ingestion and absorption, intracellular glycolysis, glycogenesis, glycogenolysis, gluconeogenesis, and glucose transport. As they put it "models relying on organizational closure can also *derive* these [homeostatic] relations [between the relevant higher- and lower-order constraints] from the underlying functional organization of the organism" (Bich et al. 2020, 10; original emphasis). Once the requirement to account for type-level part and system activity has been dropped, OA appears able to provide a function concept whose application can not only distinguish functions from accidental benefits and dysfunctions but can even underwrite modeling the relevant parts, part-activities, and system-level activities.

There are at least two things to say in response. First and less importantly, by their own admission, Bich et al. (2020, 2, 11-12) do not "provide a full-fledged model of the regulation of blood glucose concentration" but only "preliminary guidelines" for constructing such models. Second and more importantly, even if they had they provided a full-fledged model of glycemia regulation, the model could not apply to more than one system (or momentary regime of self-maintenance) without assuming a shared minimal set of regimes of self-maintenance across the relevant type. I grant that some such minimal set—one which includes regulatory mechanisms for glucose concentration in blood—exists at least for vertebrates. Thus, a model of glycemia regulation inspired by organizational principles is likely to apply across several biological taxa. But, as I argued in relation to the case of mutated Tp53, the rank heterogeneity of cancers precludes their sharing such a minimal set except possibly at extremely high levels of generality, for instance, as involving the arrest of programmed cell death. This means that models of system-level activities of cancers that are constructed following Bich and colleagues' guidelines and which appeal to functions in accordance with OA are unlikely to find application across the relevant type(s) of cancer. Yet, as Peinado and colleagues' ascription shows, cancer biologists provide functional explanations of the relevant system-level activities across the relevant type(s). If OA is to remain a descriptive account of function, it cannot recommend that cancer biologists cease giving explanations at the level of types of cancer on pain of flouting methodological adequacy.[20]

Here is an ecumenical move in anticipation of the following subsection: either the traits of cancers that have normal functions are selected to perform those functions or they are not. If they are selected to perform those functions then a modified form of OA can lean on a selected effects account of normal function to be presented immediately below. This new organizational-*cum*-selected-effects account of normal function, call it OA+SE, is similar to MA to the extent that OA+SE, like MA, makes reference to a part's contribution to an organized system's self-maintenance. On the assumption that the relevant traits are selected to perform their normal functions, OA+SE satisfies class adequacy relative to cancer biology. However,

[20] Thanks to an anonymous reviewer for this objection.

it satisfies methodological adequacy only if it is consistent with the role modeling plays in the ascription of normal function in cancer biology. On the other hand, if, as I suspect, traits of cancers with normal functions are not always or even typically selected to perform those functions then, to recover them, a proponent of OA can appeal to whatever principles seem to be at work in ascribing them in cancer biology. If I am right then they are ascribed when an activity is identified as causally relevant to an effect that is, in turn, part of how cancers of a certain type maintain themselves. And if I am right, this sort of causal relevance is (at least very often) captured through modeling the mechanism(s) that produce(s) the effect of interest. In which case, this second modified form of OA, call it OA+M, could appeal to the role modeling plays in ascribing normal functions. I do not see how going in for OA+M avoids collapse into MA.[21]

The selected effects account

Moving on, according to the standard version of the selected effects account (SE), normal functions are activities for which the function-bearing part was selected by natural selection. I consider SE for two reasons. First, because it is not explicitly tied to health such that cancers, in virtue of being pathologies, fail to have normal functions by definition (*cf.* fn.7). Second, I consider SE because at least one of its proponents has suggested that SE may be descriptive relative to cancer biology (Garson 2017a, 1100). Neander (1991a, 1991b, 2002, 2017a, 2017b) was a long-standing advocate of a descriptivist SE, claiming that the account captures at least what physiologists and neurophysiologists mean by "normal function" (2017b, especially Chapter 4). According to Neander:

> (SE) It is the/a [normal] function of an item (*p*) of [a system] (*S*) to do that which items of *p*'s type did to contribute to the inclusive fitness of *S*'s ancestors, and which caused the genotype, of which *p* is the phenotypic expression, to be selected by natural selection (1991a, 174; variables replaced for consistency).

On SE, the ascription of normal function implies that the function-bearing part as well as its disposition and/or structure should be stable across populations which share unbroken lineages of selection for the functional activity (see Neander and Rosenberg 2012, 617–622).[22] This implication is grounded in the evolutionary history of the part, which the account claims is explanatory of its function.[23] For instance, certain cells in the optic tectum of the common toad (*B. bufo*) have the normal function of responding to prey-like objects in their receptive fields because cells of that type contributed to the inclusive fitness of ancestral common toads by doing

[21] Thanks to an anonymous reviewer for pushing me to clarify this point.

[22] Thanks to an anonymous reviewer for pushing me to clarify this point.

[23] The selected effects account is not the only one inspired by evolutionary theory (see, for instance,Bigelow and Pargetter 1987; Buller 1998; Kitcher 1993). However, I leave a full treatment of those accounts for another occasion.

so and thereby caused the genotype, of which those cells are the phenotypic expression, to be selected by natural selection (Neander 1991a, 2017b). Contemporary common toads that share an unbroken lineage with the relevant population of ancestral common toads should therefore have optic tecta containing cells that respond to prey-like objects and those cells should have the dispositions and/or structural features that allow them to do so.

SE is consistent with the methodological role played by the ascription of normal function in cancer biology. It holds that normal functions are ascribed as part of the practice of modeling species. Identifying normal functions for the construction of these "species designs" depends on a variety of experimental tools. In fact, modeling itself is among these tools. For instance, modeling the mechanism(s) of prey detection, like modeling that of pre-metastatic niche formation, appears integral to ascribing normal function (Neander 2017b, especially Chapter 5). The normal functions ascribed are then represented in *further* models, namely, species designs. Models are thus given a considerable role by SE. The account stands to satisfy methodological adequacy relative to cancer biology.

Shifting focus to class adequacy, though Neander herself does not extend the ascription of normal function to pathologies (2017b, 62–63), she acknowledges that systems other than organisms might be subject to selection (2017b, 21). Bracketing the fact that they are pathologies, if cancers are among the class of systems subject to natural selection then their parts might have normal functions on SE. The account thus *appears* to satisfy class adequacy. As it turns out, a recent trend in cancer biology has seen researchers take up an evolutionary perspective on cancer. This perspective bears explanatory fruit by framing cancer progression as a process of clonal evolution (Greaves and Maley 2012; Plutynski 2017, especially Chapter5, Plutynski 2018; Bozic and Wu 2020). Cancer cells and their clonal progeny are thought to be subject to the selection pressures imposed by a hostile environment in the form of limited resources, immune response, and treatment. They are also subject to environmental constraints like the physical structure of their microenvironment. To persist and propagate, cancers must effectively balance the use of resources, expansion, and evasion (Hausser and Alon 2020). Cancers appear to meet the conditions necessary for being subject to natural selection: they exhibit inherited variation, differential fit between system and environment, and differential retention of systems or traits. Those traits that are differentially retained are selected by natural selection (Lewontin 1970). In which case, those traits have whatever normal function they were selected to perform.

Unfortunately, SE still threatens to flout class adequacy relative to cancer biology. Satisfaction of the conditions for being subject to natural selection is a matter of degree (Godfrey-Smith 2009a). And several types of cancers do not meet these conditions except minimally (Germain 2012; Germain and Laplane 2017; *cf.* Lean and Plutynski 2016). At the cellular level, the parts of cancers that are ascribed normal functions are often enough the product of genetic drift or genetic hitchhiking without necessarily being fully co-opted (Germain 2012, 806). And at the tumor level, these parts are often enough neither heritable nor recapitulated in metastases nor the product of competition (Germain and Laplane 2017, 281–287). In which case, it is

at least possible that some parts of cancers have normal functions despite not being selected for by natural selection. But, on SE, a necessary condition on a part's having a normal function is its being selected for by natural selection. Thus, allowing the ascription of normal functions to pathologies is unlikely to allow SE to satisfy class adequacy relative to cancer biology.[24]

A proponent of SE might broaden the scope of selection mechanisms beyond natural selection. Garson's generalized selected effects account does just this (2011; 2012; 2016; 2017b). Moreover, he claims that his account can capture the ascription of normal function to parts of cancers so long as those parts are adaptations or are retained or reinforced over others (Garson 2017a, 1100). Differential retention/reinforcement need not involve heritability, recapitulation, competition, or that parts be retained *after* exaptation. In fact, differential retention/reinforcement might well explain how function-bearing parts are initially co-opted in cancers. Garson's account appears able to satisfy class adequacy relative to cancer biology.

Here is an ecumenical move: a proponent of SE can combine Garson's liberal account of selection with Neander's claims concerning the role of modeling in ascribing normal functions. The resulting modified selected effects account appears to satisfy both class adequacy and methodological adequacy relative to cancer biology. The account might still exclude the ascription of normal functions to parts of cancers that benefit those cancers by means of performing the relevant activity but are not yet retained or reinforced over others. By contrast, MA does not exclude the ascription of normal functions to these parts. This is because, on MA, self-maintenance does not imply retention or replication of a part (or system) *over* that of another. MA's lowering the bar on normal function ascription is an advantage to the extent that it captures more of the normal functions ascribed in cancer biology than this Garson-Neander hybrid SE.[25]

[24] A separate but, to my mind, equally pressing issue stems from the fact that SE and other etiological accounts assume a distinction between system and environment. Drawing this distinction is especially tricky in the case of cancers such that doing so as part of the recent evolutionary turn in cancer biology is likely an idealization on the part of researchers. After all, as the case presented by Peinado and colleagues shows, the relevant system can be spatially discontinuous and distributed across the "environment"—in this case, the body. Given that distinguishing system from environment is an idealization, at least in the case of cancer, those ascriptions that rely on treating the normal functions of cancers as effects of clonal evolution are likely part of the process of modeling cancers. It is then not clear that they pick out a kind of activity that is metaphysically distinct from other kinds of part-activity. And though this may not go against the letter of accounts like Neander's, it surely goes against the spirit of such accounts. For an argument to this effect and an independent argument favoring the application of organizational accounts of function to cancer, see Bertolaso (2013).

[25] It is open to a proponent of the Garson-Neander account to dispute whether exapted parts that have not become adaptations have any normal functions. In fact, a proponent of the Garson-Neander view might well claim that, prior to retention/reinforcement, the relevant activities are at most systematic/causal role functions (fn.7). Addressing this claim goes beyond the scope of this paper.

Objections: loose talk and going wrong

I have so far argued for MA's superiority as a descriptive account of normal function relative to cancer biology. Here, I consider and respond to two possible objections to the claim motivating my argument, namely, that cancer biologists ascribe normal functions to parts of cancers. Each objection corresponds to class adequacy and methodological adequacy. First, one might claim that cancers are just not the type of system that can appropriately be ascribed normal functions. Any appearance to the contrary reflects a loose way of speaking on the part of some cancer biologists. In which case, MA is overly broad relative to cancer biology. I call this "the objection from loose talk." Second, one might allow that parts of cancers are ascribed normal functions but deny that what is being explained are the contributions those parts make to the self-maintenance of the cancer. Rather, the ascription serves to identify the normal function of healthy variants in the context of pathology. In which case, MA mislocates the relevant explanandum in cancer biology. I call this "the objection from going wrong."

The objection from loose talk

Starting with the objection from loose talk, one might claim that cancer biologists do not ascribe normal functions to parts of cancers at all. This objector claims that there is no reason to think that the ascription of "the function" or "the novel function" to a part of cancer identifies a standard for its activity, dispositions, or structure. At most, these functions, like those ascribed in cladistic systematics, identify actual or typical causes of disease progression. Moreover, cancer biologists appear to reserve talk of "normal function" for the activities of healthy variants when contrasting those activities with that of parts of cancers.

In response, there is at least one reason for trying to identify standards for part-activity, dispositions, and/or structure among types of cancers. Namely, doing so successfully provides viable avenues for treatment in virtue of predicting and/or explaining how types of cancer achieve self-maintenance. The ultimate aim of cancer biology is the development of effective clinical interventions. As we have seen, this aim is problematized by the heterogeneity that cancers exhibit. And it is further problematized by cancers effectively exploiting that heterogeneity. The result is that the more thoroughly a cancer establishes itself in its host the more specialized the knowledge required to undermine its deleterious features becomes. At the same time, the heterogeneity that cancers exhibit and exploit is limited by the evolutionary history of the organism, the mutations driving the cancer, the rate at which the cancer mutates, the organism's environment, and much more besides. These limits do not group traits into anything resembling unified kinds but can be used as guideposts to

common vulnerabilities among cancers. The plurality of classificatory schemes and scientific tools like modeling allow researchers to find and exploit these common vulnerabilities in a principled way. I submit that knowledge of how to undermine particular traits or mechanisms across types of cancer is often gathered by modeling those traits and mechanisms under the guise of normal function. These models cut across instances in which the relevant parts or mechanisms fail to benefit the cancer. This is partly because clinicians do not necessarily want to rectify those failures. Nonetheless, in seeking to undermine the disease, the models cancer biologists build capture standards for the activities, dispositions, and/or structural features of those parts. And they do so effectively by employing the notion of normal function.

I want to stress that giving up on normal functions here threatens to deprive us of an extremely useful explanatory tool in the cancer biologist's toolbox. Even if their ascription is an in principle dispensable part of cancer biology, the case presented by Peinado et al. (2012) shows that normal functions serve as an effective guide to at least some commonalities of clinical significance among cancers. Peinado and colleagues are not alone in this practice. Indeed, cancer biologists have ascribed a number of pro-oncogenic, pro-tumorigenic, and pro-metastatic functions to signaling and receptor proteins, catalyzing enzymes, lipoproteins, growth factors, and so on (Goel and Mercurio 2013; Bång-Rudenstam et al. 2019; Gerlach and Weigmann 2019; Ilhan et al. 2020; Peng et al. 2020; Yu et al. 2020). Cancer biologists in this emerging tradition aim to predict and/or explain the way these parts benefit cancers through those parts' activity *at the type-level* and, unsurprisingly, aim to discover the dispositions and structural features by which those parts benefit those cancers, again, *at the type-level*. This is because discovering these type-level dispositions and features give those working in precision oncology a clinical foothold in the form of targets for intervention. Moreover, knowing that the relevant part of an individual cancer is not performing its normal function can aid in the discriminatory use of the relevant interventions, making precision oncology that much more precise (and effective). This is exactly what we should expect if MA is right: it is the role of normal functions to tell us what these parts are supposed to do. In this case, their doing so allows us to undermine those parts' ability to do what they are supposed to.[26]

I suspect that resistance to allowing normal functions to be ascribed to parts of cancers rests partly in conflating distinct (albeit related) categories of biological normativity: normality and health.[27] Health is a state that is good to be in. And what is

[26] Thanks to an anonymous reviewer for pushing me to clarify this point and allowing me the opportunity to stockpile these examples in the main text.

[27] Part of what is at issue in this discussion is how cancer biologists talk about the activities of parts of cancers. However, it would be premature to claim that because cancer biologists often use "normal" to talk about healthy activities in contrast to pathological ones it follows that they do not ascribe normal functions to parts of cancers, where normal functions embody a standard for part-activity, disposition, and/or structure.

healthy is conducive to being in that state. The heart's pumping blood (efficiently) is healthy. But health is not synonymous with normality where normality merely sets standards among a type of system (*cf.* Boorse 1977). Consider an Olympic cyclist whose leg muscles are quickly atrophying. The state of his leg muscles is unhealthy despite crossing into what is normal for human beings (of his age and sex) on a number of dimensions, e.g., volume or mass, as they wither. By contrast, a second Olympic cyclist in her prime will have leg muscles that differ from what is normal on those dimensions and many besides. Normality and health can come apart. Normality sets standards across types of system and some parts of cancers exhibit activities, dispositions, and/or structural features that embody those standards. That cancers are pathological and that cancer biologists often use "normal" to mean healthy in no way undermines the propriety of ascribing normal functions to parts of cancers.

The objection from going wrong

The objection from going wrong allows that cancer biology exhibits the ascription of normal functions to parts of cancers. However, the objector denies that the normal functions ascribed are activities that contribute to the self-maintenance of any pathology. Rather, in every case, they are activities that would contribute to the organism but are performed in an unfortunate context. Following Matthewson and Griffiths (2017), I consider this a way of "going wrong" in the sense of violating some biological norm. Matthewson and Griffiths list four ways of going wrong: (i) malfunction (i.e. pathology), (ii) performance of a normal function in a non-hostile environment that is nonetheless alien and/or systematically impedes performance (2017, 454) (iii) performance of a normal function in a hostile environment, and iv) performance of a normal function in a non-alien, non-hostile environment that is nonetheless unlucky.

In the case of cancer, the objector might say that cancers are nothing more than ways of going wrong for the organisms that contract them. Any ascription of a normal function to a part of cancer is at most a recognition of the activity which that part is supposed to perform in healthy variants. The activity of sEV in melanoma progression is not functional because it promotes tumor growth and metastasis. It is functional only because it aids the growth of vascular tissue and immune response in healthy individuals (Neander 2017a, 1155, fn.24). Unfortunately, in the case presented by Peinado et al. (2012), vascular growth and immune response occur in light of the activity of cancerous cells. That is why sEV activity in the case presented above is considered both functional and pathological: sEV are doing what they are supposed to do but in an alien, hostile, or unlucky context. So, the objection goes, there is no ascription of normal functions to parts of cancers just as such. There is only the ascription of normal

functions to parts of non-pathological systems whose performance sometimes, unfortunately, ends up promoting pathologies.

In response, it is often the case that the activities performed by parts of cancers are the same as or similar to those performed by healthy variants. However, even when this is the case, these overlapping activities are not necessarily what is being identified as a normal function. Claiming otherwise threatens to belie the object of research of which Peinado et al. (2012) is a representative example, namely, identifying what parts of cancers standardly do *for those cancers*. The normal functions ascribed to sEV, microRNAs, co-opted cells, etc. make contributions that are key to carcinogenesis, tumorigenesis, and metastasis. Moreover, when the relevant activity is *not* found among healthy variants, the function is labeled "novel." MA can capture both of these facts: the activity is identified as a normal function by figuring out, ideally by means of modeling, how its performance contributes to the relevant type of cancer, specifically to self-maintenance across that type. Thus, it is not the case that the ascription of normal functions to parts of cancers is no more than the recognition of the exercise of normal functions of healthy variants "going wrong."

I suspect the temptation to assimilate normal functions of parts of cancers to overlapping activities of healthy variants rests partly in an attempt to hold onto metaphysical unity among normal functions. Several philosophers are committed to the claim that the category of normal function is real or mind-independent (for instance, Neander 2017b, especially Chapter 3). This means that the kind of activity identified with those functions is metaphysically distinct in virtue of having a certain property or properties, say, being selected for, being species-typical, having a particular purpose within the organism, etc., which other kinds of activity lack. If so then that property or those properties stand(s) to bear epistemic fruit and to have certain normative upshots. However, this hope belies an overly simplistic view of explanatory categories in science and threatens to get in the way of clinically significant discovery. As we saw in the "Assessing other accounts of normal function" section, attempts at analyses of normal function in terms that set them apart metaphysically ran into difficulties accounting for application of the concept by cancer biologists. Moreover, many explanatory categories in science do not admit of conceptual analysis, including the category of cancer itself (Plutynski 2018)! Rather than forcing consistency in the name of identifying a kind of activity at the metaphysical level, philosophers working in the literature on function should use cases like that discussed in this paper as an opportunity to seriously reflect on the higher-order goals of supplying a unified account of normal function.

Conclusion

I have argued that we need an account of normal function that satisfies class adequacy and methodological adequacy relative to cancer biology. I claimed that the Modeling Account of Normal Function does so and applied it to what I take to be a paradigmatic example of cancer biologists ascribing normal functions to cancers. Other accounts of normal function struggle but can be modified to capture at least some of the normal functions these researchers ascribe. Whatever account is best suited to explicate the ascription of normal function to parts of cancers, that we need

one has at least one upshot for the philosophy of biology. The contemporary literature on function has been around for a half-century. Yet, there has been little sustained discussion of the functions—normal or otherwise—of complex pathologies except as counterexamples. This is the case despite there being ample evidence that, say, cancer biologists ascribe normal functions to parts of pathologies. While some might claim that the lack of discussion is due to pathologies being processes that are contrary to normality at the metaphysical level (Boorse 1977, 1997; Garson 2013), I believe it is a product of an overemphasis on the study of organisms. Organisms are an important object of study in biology. However, part of what is interesting about organisms is not distinctive of them, namely, that they are organized in ways that allow them to sustain themselves. Others have drawn on this common feature of biological systems to make sense of the ascription of function to, for instance, ecosystems (Nunes-Neto et al. 2014; Dussault and Bouchard 2017; Morrow forthcoming). MA attempts to draw on these commonalities to make sense of the ascription of normal functions to parts of cancers. Regardless of whether the account succeeds, this paper will have served its purpose if it galvanizes philosophers to find an account of function that carves Nature at her "oncological joints."[28]

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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