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Functional homology and homology of function: biological concepts and philosophical consequences

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Abstract "Functional homology" appears regularly in different areas of biological research and yet it is apparently a contradiction in terms—homology concerns identity of structure regardless of form and function. I argue that despite this conceptual tension there is a legitimate conception of 'homology of function', which can be recovered by utilizing a distinction from pre-Darwinian physiology (use versus activity) to identify an appropriate meaning of 'function'. This account is directly applicable to molecular developmental biology and shares a connection to the theme of hierarchy in homology. I situate 'homology of function' within existing definitions and criteria for structural assessments of homology, and introduce a criterion of 'organization' for judging function homologues, which focuses on hierarchically interconnected interdependencies (similar to relative position and connection for skeletal elements in structural homology). This analysis of biological concepts has at least three broad philosophical consequences: (1) it provides the grounds for the study of behavior and psychological categories as homologues; (2) it demonstrates that philosophers who take selected effect function as primary effectively ignore large portions of comparative, structural, and experimental research, thereby misconstruing biological reasoning and knowledge; and, (3) it underwrites causal generalizations, which illuminates inferences made from model organisms in experimental biology.

Keywords Activity · Developmental biology · Epistemology · Function · Homology · Structural biology

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The very idea

"Functional homology" appears regularly in biological, psychological, and philosophical literature. In molecular developmental genetics, the conserved role of homeobox genes in axial patterning is referred to as functionally homologous (Manak and Scott 1994), over and above the relation of structural homology that obtains between DNA sequences. In comparative psychology, behavioral and cognitive homologues are routinely invoked (Hauser 2005). In philosophical discussion, it has been claimed that function is a necessary aspect of character individuation involved in homology assessments (Neander 2002). And yet 'functional homology' is a contradiction in terms, or so many structural biologists would claim (Abouheif et al. 1997). Over 150 years ago, Richard Owen defined homology as identity of structure regardless of form and function (Owen 1843). The descendant, evolutionary distinction between homology (structure) and analogy (function) is founded on this recognition. Therefore, the very idea of functional homology appears theoretically confused and there is conceptual tension in its utilization by biological researchers.

The title of the paper is meant to signify a shift away from the problematic usage of 'functional homology' to a technical idea of 'homology of function' that respects these existing distinctions and does not contradict comparative biology's concepts and methods. My philosophical analysis is not meant to justify every instance of "functional homology" (because many are illegitimate), but instead demonstrates that there are both reasons to have an appropriate conception and philosophical consequences to its explicit articulation. First, I treat the tension inherent in 'functional homology' and the rationale behind a project that attempts to alleviate it. Second, I use a pre-Darwinian physiological distinction between two different types of function (use versus activity) to isolate the appropriate meaning of 'function' for homology, which thereby eliminates the conceptual tension. Third, I explore examples from molecular developmental genetics to illustrate the value of these distinctions in 'experimental biology' (Weber 2005) and uncover the significance of hierarchy for 'homology of function'. Fourth, I situate the account in the theoretical context of homology and introduces 'organization' as a putative criterion for discerning homology of function. The relative position and connection of homologous functions in organized, hierarchical relationships is equivalent to the relative position and connection of skeletal elements used to determine structural homology.

Three broad philosophical consequences result from this analysis of homology of function. First, it provides a clearer analysis of functional characters, such as behavior or psychological categories studied in philosophy of mind and psychology (Ereshefsky, this issue; Griffiths 1997, 2007; Matthen, this issue). Second, it demonstrates that selected effect function plays a subordinate role in much of comparative, experimental, and structural biology, as well as often being theoretically inappropriate (but see Matthen, this issue). Philosophers who hold that selected effect function is implicit in all character individuation misconstrue key aspects of evolutionary research, and the structure of biological knowledge more generally. Third, it underwrites causal generalizations, which illuminates inferences made from model organisms in experimental biology. The functional dynamics of model systems can be legitimately extrapolated across phylogenetic distances to the degree that homology rather than analogy characterizes those functions.

Identifying the tension and motivations for its resolution

What exactly is the tension in the idea of functional homology? Owen's original definition of a homologue is "the same organ in different animals under every variety of form and function" (Owen 1843: 379). The reference to organ is indicative of a structure (an entity) found in an organism that may vary in its shape and composition (form) or what it is for (function) across the organisms where it occurs. Translated into an evolutionary context, 'sameness' is cashed out by reference to common ancestry. Since structures can also be *similar* by virtue of natural selection operating in similar environments, homology needs to be contrasted with analogy. Homologous structures are the *same* by virtue of descent from a common ancestor, regardless of what functions these structures are involved in, whereas analogous structures are *similar* by virtue of selection processes favoring comparable functional outcomes, regardless of common descent. This is what makes similarity of function an especially problematic criterion of homology in genes or other structures (Abouheif et al. 1997). Because similarity is the appropriate relation for analogy, it is not necessary for analogues to have the 'same' function as a consequence of common ancestry—similarity despite different origins suffices (Ghiselin 2005). Classic cases of analogy involve taxa that obviously do not share a recent common ancestor with the structure, such as the external body morphology of dolphins and tuna (Pabst 2000). Functional homology is thus a kind of category error because what a structure does should not enter into an evaluation of homologue correspondence and similarity of function is often the result of adaptation via natural selection to common environmental demands, not common ancestry.[1] The juxtaposition of 'function' and 'homology' is oxymoronic, if not a contradiction in theoretical terms.

A natural strategy in response to the identification of this conceptual tension is terminological expulsion; there is no such thing as 'functional homology' and biologists should refrain from invoking it. But there are at least two reasons not to go this route. First, a variety of evolutionary researchers have pursued the identification of behaviors (functions) that are homologous (Ereshefsky, this issue; Greene 1994; Wenzel 1992). This has historical precedent in the research of ethologists such as Konrad Lorenz, and makes sense theoretically; some behavioral repertoires are present as a consequence of common descent. Formally, entities that have the same function are not automatically analogues resulting from convergence due to adaptive natural selection (cf. Ghiselin 2005). Constriction behavior in snakes can be seen as a homologous function, especially once set in a phylogenetic context (Greene and Burghardt 1978).

A second reason to not simply throw out 'functional homology' is its widespread use in molecular and developmental biology, as the following article titles indicate.

> Structural and functional homology between duck and chicken interferon-gamma (Huang et al. 2001)
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> Functional homology among human and fission yeast Cdc14 phosphatases (Vázquez-Novelle et al. 2005)
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> Phasic cholinergic signaling in the hippocampus: functional homology with the neocortex? (Gulledge and Kawaguchi 2007)

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[1] Many biological cases are tricky to interpret and the line between homology and analogy can be difficult to draw in practice, especially because of the hierarchical relationships among homologues and analogues (Hall 1994). The contrast class for homology is often taken to be more than analogy (convergent similarity of function due to selection). 'Homoplasy' encompasses analogy, reversal, parallelism, and other non-homologous phenomena (Hall 2003).

Functional homology between yeast piD261/Bud32 and human PRPK: both phosphorylate p53 and PRPK partially complements piD261/Bud32 deficiency (Facchin et al. 2003)

Structural/functional homology between the bacterial and eukaryotic cytoskeletons (Amos et al. 2004)

Even when "functional homology" is not explicitly used, the terminology is nearly equivalent (albeit somewhat tortured): "this might indicate some orthologue [gene homologue] functional relationship between these two subclasses, even if [they] share only a low degree of sequence homology" (Pohl and Knöchel 2005: 26). But while it is important to recognize this widespread use of functional homology, some of these occurrences may be illicit. Swapping structurally homologous genes between species to rescue mutant or null phenotypes is not a genuine criterion of functional homology, especially when there is little or no attention to establishing a phylogenetic context. This makes many claims of functional homology between model organisms suspect (e.g. Vázquez-Novelle et al. 2005).

A final motivation for explicating 'homology of function' arises out of the aim to have systematic relations between aspects of explanatory reasoning in biology. One well known characterization of evolutionary novelty invokes a criterion of non-homology: "A morphological novelty is a structure that is neither homologous to any structure in the ancestral species nor homonomous [serially homologous] to other structures of the same organism" (Müller and Wagner 1991: 243). Elsewhere (Love 2005, 2006), I have distinguished evolutionary novelty from innovation with the former referring to the origin of new *forms* and the latter referring to the origin of new *functions*.[2] A parallel characterization of evolutionary innovation can then be stated: "An organismal innovation is a function that is neither extant in the ancestral species nor operational elsewhere in the functional context of the same organism" (Love 2005: 84). Parsing these conceptual differences facilitates a more precise reconstruction of the criteria of explanatory adequacy involved in biological explanations of innovation and novelty. But without an account of homology of function, the characterization of evolutionary innovation is problematic because it presumes an assessment of 'functional' *non*-homology.[3] Thus, resolving the tension in 'functional homology' is also motivated by its connections to other biological concepts.

While it is clear that the concept of homology per se differs in its meaning as a consequence of diverse explanatory ends in different areas of research (Brigandt 2003), the three distinct motivations (prior studies of behavioral homology; widespread use in molecular developmental genetics; the connection with evolutionary innovation) encourage the search for a legitimate account of homology of function. These motivations are anchored in a philosophical commitment to first understand actual reasoning patterns in a science before attempting a general account of its concepts (if at all); i.e. it is a criterion of adequacy to comprehend the common commitment to some idea of 'functional homology' across different biological disciplines. This demands attention to the heterogeneity of conceptual use while encouraging the search for interconnections across disciplinary approaches that may lead to a more unified perspective.

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[2] Form is explicated in terms of the material composition and arrangement, shape or appearance of organic materials (Bock and von Wahlert 1965), whereas function picks out activities at any level of organization performed or displayed by organisms (Dullemeijer 1981).

[3] Strictly parallel language displays this dependence: 'an organismal innovation is a function that is neither homologous to any function in the ancestral species nor operational elsewhere (serially homologous) in the functional context of the same organism'.

‘Function’ in philosophy and an old physiological distinction

One of the most contentious areas of debate in philosophy of biology concerns functional ascriptions (e.g. Allen et al. 1998; Ariew et al. 2002; Davies 2001; Lewens 2004). Through specific attention to the heterogeneity of concept use in actual scientific practice, Arno Wouters (2003, 2005) distinguishes four separate meanings of ‘function’ in biology: activity (what something does), causal role (contribution to a capacity), fitness advantage or viability (value of having something), and selected effect or etiology (origination and maintenance via natural selection). Debate has raged about which of them (if any) is most appropriate for different aspects of biological and psychological reasoning or most general in scope (i.e. what makes them all ‘function’ concepts?). For our purposes, these four meanings broadly capture what *might* be in view when biologists appeal to functional homology.

If we are to avoid the conceptual tension that involves mixing together homology and analogy, then the appropriate notion of function cannot be based on selection history, which is allied with the concept of analogy and concerns a particular variety of function (that variety which is selected). Similarly, viability interpretations concentrate on features where the particular variety of function is critical because of conferred survival advantages. Any interpretation of function that relies on a particular variety of function (because it was selected or because it confers viability) clashes with the demand that homology concern something ‘under every variety of form and function.’ This leaves activity and causal role interpretations, which might be expected since they are commonly utilized in structural biology (Amundson and Lauder 1994; Bock and von Wahlert 1965; Dullemeijer 1981). But a causal role interpretation emphasizes a systemic capacity to which a function makes a contribution; i.e. causal role functions also focus on a particular variety of function, though in a way different from either selected effect or viability interpretations. Only an activity interpretation (‘what something does’) accents the ‘function’ itself, apart from its specific contribution to a systemic capacity and position in a larger context. Therefore, the appropriate meaning for ‘homology of function’ is activity not causal role, since activity can remain constant ‘under every variety of form and function’. An evaluation of sameness due to common ancestry is made separately from the role the function plays, whether understood in terms of a causal role, a fitness advantage, or a history of selection. We need an interpretation of function in terms of ‘what it is’ rather than ‘what it is for’, and function as activity fits the requirement.[4]

A difficulty of having four distinct meanings for functional ascriptions is that the term “function” is weighed down by polysemy. Introducing adjectival modifiers can attenuate this and capture the distinction relevant for homology of function. Although there has not been a universal commitment to recovering pre-Darwinian talk of ‘function’, there has been some discussion about whether current interpretations can be related to older usage (cf. Lewens 2004; Millikan 1989; Neander 1991). What has been overlooked, in part because of seeing the key dividing line in terms of Darwin and natural selection, is that many students of physiology already had subtle distinctions that separated different senses of function. One of the most prominent of these, a distinction between ‘use’ and ‘activity’, can be found in the work of Galen (Furley and Wilkie 1984: 58–69).[5] The functional *use* of

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[4] Bock and von Wahlert (1965) made a similar distinction between ‘activity’ (what something does) and ‘biological role’ (what something is used for). I originally took their ‘activity’ to correspond to causal role functions (Love 2005, 2006), but now concur that they are distinct (see Wouters 2003: 642–3).

[5] This distinction came to my attention via an unpublished paper by Jim Lennox entitled “Biological function: a brief slice of history”. There is a third aspect, ‘movement’, which I am ignoring here.

Table 1 Different distinctions regarding 'function'

Function	Use 'What it is for'	Activity 'What it is'
Selected effect	✓	
Viability	✓	
Causal role	✓	
'Mere' activity		✓

Classification of four different interpretations of function in contemporary biology (Wouters 2003, 2005) according to the ancient use versus activity function distinction. Notice that the two main rivals in recent philosophical literature, selected effect and causal role, are both categorized as use-functions (what something is for) in contrast to activity-function (what something is or does)

a physiological feature represents 'what it is for' whereas the functional *activity* of a physiological feature picks out 'what it does' (or how it works). Multiple activities might underlie a particular use and one activity may be in the service of multiple uses; the terms do not have equivalent extensions. They are also not equivalent epistemologically because we may know what something does but not what it is for and, alternatively, what something is for but not how it accomplishes this.[6]

I propose resurrecting this terminology as modifiers of the term 'function' to make clear the appropriate sense for homology (Table 1). *Use*-function can correspond to causal role, viability, or selected effect functions, although causal role may be the most relevant for historical interpretation. But Galen's *activity*-function closely maps to what Wouters calls 'mere' activity and does not invoke a specific variety of functional contribution.[7] Therefore, although use-functions understood as causal roles could relieve the tension in 'functional homology' by removing the reference to selection or fitness advantage (a strategy implied by some functional morphologists; see Amundson and Lauder 1994), activity-function is more appropriate because of its focus on the homology of activities themselves apart from their particular uses. It unambiguously removes the tension that plagues the concept of functional homology to generate a legitimate notion of 'homology of function'—the same *activity-function* in different animals under every variety of form and *use-function*. There is a place for the causal role interpretation in assessments of homology, but it pertains to the criteria rather than definition of homology. Before seeing this we need to observe activity-function homology in vivo.

Hierarchy and activity-function homology in molecular developmental genetics

Careful discussions of regulatory gene function in development and evolution recognize something akin to the distinction between activity- and use-function; i.e. between what a gene does and what it is for in some larger process within the organism.

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[6] "Explanations of use and explanations of activity will refer to quite different sets of facts; and this is as true today as it was for Galen" (Furley and Wilkie 1984: 63).

[7] It should be stressed that the use vs. activity distinction is epistemological, which means that there need not be 'bare' activity-functions with no use-function. Rather, activity-functions can be described and investigated as such apart from their use-functions, whether causal role, viability, or selected effect. There can also be different descriptions of the same activity-function that may be more or less germane depending on which use-functions are in view.

> When studying the molecular evolution of regulatory genes, their biochemical and developmental function must be considered separately. The biochemical function of *PAX–6* and *eyeless* are as general transcription factors (which bind and activate downstream genes), but their developmental function is their specific involvement in eye morphogenesis (Abouheif 1997: 407).

The biochemical function is the activity-function and the developmental function is the use-function. This contrast is becoming more widely acknowledged. In a review of *Hox* genes and their gene targets in mammals, Svingen and Tonissen (2006) distinguish transcriptional specificity from functional specificity, where the former refers to the biochemical function of DNA binding and the latter refers to the developmental function played by the transcription factor. In practice these two are often equated for *Hox* genes because initial evidence pointed to their coincidence; their activity appeared to be uniquely associated with one causal role. But the distinction between biochemical and developmental function in genes should be strictly observed because it also discriminates between divergent evolutionary trajectories.

> The biochemical function of these genes is highly conserved through evolutionary time, while their developmental function is relatively free to vary. This inherent property of developmental regulatory genes allows them to be independently co-opted to function in structures which clearly have independent evolutionary origins (Abouheif 1997: 407).

Biochemical *activity*-functions of genes are often conserved (i.e. homologous), while simultaneously being available for co-option to make causal role contributions (*use*-functions) to distinct developmental processes. The same regulatory genes are evolutionarily stable in terms of activity-function and evolutionarily labile in terms of use-function. By implication, claims about use-function homology for genes *qua* developmental function are more suspect than those concerning activity-function homology for genes *qua* biochemical function because developmental functions are more likely to have changed as phylogenetic distance increases. Although this keeps the air conceptually clear, it renders many claims of functional homology problematic since, to seize one prominent example, the conserved roles of homeobox genes in axial patterning or morphogenesis (i.e. developmental use-functions) are referred to as functional homologues across all metazoans (Manak and Scott 1994).

Part of the solution required to legitimately interpret these cases is the recognition that hierarchical aspects of homology apply to activity-functions just as much as structures (Abouheif 1997; Hall 1994). Morphological homologies remain despite alterations in their composition or developmental origin (Brigandt 2006, this issue; Griffiths 2006; Wray 1999). The neural tube is a homologue across all vertebrate animals but arises from distinct processes involving divergent patterns of gene expression in different taxa (e.g. folding over of a layer of tissue in amphibians versus the hollowing out of a solid rod in bony fish). We should also expect that functional homologies persist despite different developmental origins or components. Our formulation encourages it explicitly—the same activity-function in different animals *under every variety of form* and use-function—directing us to consider the same function in the face of alterations in the appearance and arrangement of structural materials. This fits with the argument of ethologists and functional morphologists that homology of function is not directly parasitic on homology of structure (Ereshefsky, this issue; Lauder 1994; Wenzel 1992). We need to shift our perspective within these hierarchies along with the meaning of function. In order to reinterpret these problematic claims about functional homology in developmental processes, the capacity defining the use-function of a regulatory gene at one level of organization, such as axial patterning, must be considered as an activity-function itself at another level of organization, such as the differentiation of serially repeated elements along a body axis. Note that 'level of organization' need not be compositional in nature and thus the language of 'higher' and 'lower' levels may be inappropriate. Functional or procedural hierarchies may not differ in their structural level of organization but, for example, in temporal ordering (see Wimsatt 2002 for discussion).[8] The developmental roles of homeobox genes in axial patterning may be conserved by virtue of their biochemical activity-function homologies but homeobox genes are not use-function homologues because of these developmental roles. Instead of focusing on the activity of a gene component and its causal role in axial patterning we shift to the activity of axial patterning and its causal role elsewhere (or elsewhen) in embryonic development.[9]

The complexity of hierarchy is observable even within regulatory genes themselves. Worries that the activity of DNA binding by *Hox* genes is not uniquely associated with one developmental role (i.e. transcriptional and functional specificity not coinciding) arise from accumulating evidence for their divergence. For example, *NK-2* genes are involved in mesoderm specification, which underlies muscle morphogenesis. In *Drosophila*, the expression of a particular *NK-2* gene (*tinman*) is critical for both cardiac and visceral mesoderm development. If *tinman* is knocked out and transgenically replaced with its vertebrate orthologue *Nkx2–5*, only visceral mesoderm specification is rescued; the regulation of cardiac mesoderm is not (Ranganayakulu et al. 1998). A region of the vertebrate protein near the $5'$ end of the polypeptide differs enough to prevent appropriate regulation in cardiac morphogenesis. The homeodomains for vertebrate *Nkx2–5* and *Drosophila tinman* (the stretch of sequence that confers DNA binding) are interchangeable and this is one reason researchers were led to the 52 amino acids at the N-terminus of the polypeptide. The inability of *Nkx2–5* to rescue cardiac mesoderm specification is *not* related to the activity-function of differential DNA binding. One component of the orthologous proteins in both species retains an activity-function homology related to visceral mesoderm specification but another component (*not* the homeodomain) has diverged. This type of homeobox gene does not have a single use-function (as expected) but it also does not have a single activity-function. Any adequate evaluation of this case and others must recognize a more fine-grained decomposition into functional units within the 'gene' to capture genuine activity-function conservation.[10]

The case of activity-function homology in homeobox genes suggests caution in how we parse 'levels' relevant to both structural and activity-function homologues. An open reading frame is a decomposable unit of the genome within which are contained at least two further component homologues in the case of *NK-2* genes: the DNA binding motif and the sequence involved in the relevant protein-protein interaction required in cardiogenesis.

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[8] Activity-function homology and the nature of functional hierarchies are related to explorations of 'process homology' by Evo-devo researchers: "By a 'process' we refer to an action (*what* happens), not to its functional outcome (*why* it happens)" (Gilbert and Bolker 2001: 445; see also Brigandt, this issue).

[9] There is no privileged level of analysis; only the requirement that one is explicit about where you are trying to discern activity-function homologues. Thus, even though rhythmic muscular contraction is an activity that contributes to the causal role capacity of the heart pumping, heart pumping could be considered as an activity-function homologue in the causal role context of the cardiovascular system.

[10] One key explanation for this divergence in developmental role despite activity-function homology of DNA binding is that *Hox* genes work in tandem with other cofactors (Svingen and Tonissen 2006). Change in sequence outside of the DNA binding domain can lead to altered cofactor interaction, which implies that a regulatory gene can retain one activity-function homology and lose another.

We can link activity-function homologues directly to structural motif homologues but there is no single activity-function for the entire open reading frame. This reveals why the claim about homeobox genes being ‘functional homologues’ is confused. Considering the regulatory gene as a use-function homologue in axial patterning often means aggregating all of the activity-functions from an open reading frame. Structural and functional individuation can be decoupled, even in cases with the appearance of strong coupling. The diversity of hierarchical relationships relevant to activity-function homology illustrated in this decoupling also means acknowledging that relevant differences of individuation are likely to increase once more ‘levels’ are taken into account (cf. Lauder 1995).

Our discussion of activity-function homology in experimental biology indicates that hierarchy is just as relevant a phenomenon, and just as complex, as has been emphasized for structural homology (Brigandt, this issue). This is critical for the extension of activity-function homology to behavior and psychological categories (see Ereshefsky, this issue; Matthen, this issue; Wenzel 1992). Because of the decoupling of functional and structural individuation, the mixing of functions and structures purported to have some hierarchical relationship pertinent to homology is dangerous. Do we only treat ‘lower’ level functions as parts of ‘higher’ level functions or can we say that ‘higher’ level functions are composed of both functional and structural ‘components’? These are non-trivial decomposition problems that must be addressed in actual investigative practice (Lauder 1994), but activity-function homology provides a conceptual point of departure from which to approach these operational difficulties.

Definitions and criteria for activity-function homology

Having recovered a meaning for homology of function in terms of activity that resolves the tension inherent in ‘functional homology’, and seen how it can be applied to reasoning in experimental biology, we have partially fulfilled our aims of comprehending conceptual practice and articulating systematic relations between concepts of homology, analogy, and function. There remains a task of situating activity-function homology within the wider context of biological theory and structural biology methodology. The first issue to address is the *definition* of homology and the second is the *criteria* used to establish it.

Three different strategies for a definition of homology can be identified: taxic, transformational, and developmental (Brigandt 2002; Donoghue 1992). Taxic definitions equate homology with synapomorphy (shared, derived characters) in phylogenetic systematics. Transformational definitions focus on tracing structures back to a common ancestor. Developmental definitions highlight the ontogenetic mechanisms that retain and constrain homologues to reliably reappear every generation. Although these are often presented as mutually exclusive definitions, they can also be construed as complementary *characterizations* (see Brigandt, this issue). Homology is something that involves a clear phylogenetic context, tracing structures back to a common ancestor, and understanding the developmental context for their stable reproduction each generation. George Lauder has emphasized cladistic classification for homology of function judgments, especially to address the decoupling of structural and functional individuation: “Restricting the definition of homology to structures or basing homology of nonstructural characters on an analysis of morphology is unnecessary if an explicitly phylogenetic [taxic] definition of homology is used” (Lauder 1994: 152). But this perspective does not rule out the need to consider homology in terms of tracing activity-functions back to a common ancestor or understanding developmental mechanisms underlying their reliable ontogenetic construction.

Activity-function homology is largely neutral on these differences, embracing their complementarity as characterizations, with one stipulation. A phylogenetic definition of homology is necessary but insufficient for activity-function homology. Shared, derived characters (synapomorphies) are not equivalent to homologies in part because the absence of a feature can be a synapomorphy, which is a reminder that a phylogenetic context is formally established by scoring character *states*, not characters (cf. Brigandt, this issue; Ghiselin 2005; Müller 2003). Homology is an equivalence relation between *entities* (not the absence of entities) that strictly correspond to one another. (This means homology judgments, even regarding activity-functions, will be transitive; analogy assessments made on the basis of similarity are intransitive.) 'Sameness' is a result of common ancestry and/or developmental constraints so that the equivalence relation between homologues has a causal basis. Any account of activity-function homology must incorporate a version of sameness based on underlying causal processes. Taxic homology does not do this, and so it alone is insufficient for homology of activity-functions.

A second theoretical aspect concerns the criteria for identifying homologues of function. Correspondence relations among structurally homologous features are established by criteria such as relative position and/or connection, similarity of structural detail, special quality, and embryological origin. Variant forms of these criteria are also applicable to activity-functions with special quality being particularly relevant for behaviors that are complicated and distinctive (Ereshefsky, this issue; Matthen, this issue; Wenzel 1992). Because hierarchy is just as pertinent to assessments of activity-function homology, it would be ideal to recognize it in our criteria. A parallel criterion in terms of similarity of functional detail would have to be highly defeasible and recent difficulties encountered by the embryological criterion because of hierarchy (see previous section) also apply to activity-function homologues. Special quality presents its own difficulties outside of complex, stereotypical behaviors (Wenzel 1992). Together these suggest exploring a criterion that plays a role analogous to that of relative position in structural homology judgments, which would be profitable for actual research attempting to establish the requisite correspondence relations among activity-functions.

Given these considerations, one candidate for a criterion is 'organization'.[11] It involves functional determinations analogous to relative position and connection, as well as showing thematic links with 'similarity in structural detail'. Organization refers to how activities are arranged so as to contribute to causal roles, and therefore is a kind of natural evidence for activity-function homology. Organization also takes into account same level and inter-level relationships, which means it is sensitive to diverse hierarchical characterizations (Bechtel and Richardson 1993; Wimsatt 2002). Structural homologues exhibit stability in part by hierarchically interconnected interdependencies like the arrangement of and linkage among components (Müller 2003), and the extension of this idea to function is reasonable. 'Component' activity-functions are homologous because of interconnected interdependencies within a larger system, including both structural organization (e.g. part-whole hierarchies) and functional organization (e.g. temporal hierarchies). Once a phylogenetic context is established and appropriate 'levels' are attended to (structural, temporal, etc.), homologies among activity-functions can be assessed in terms of these organizational properties. Just as we look for the relative position and connection of skeletal elements when trying to judge structural homology, we fix on the relative position and connection of activities in organized, hierarchical relationships to judge activity-function homology. In philosophical terminology,

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[11] In recent literature, Gerd Müller (2003) has emphasized the importance of organization for structural homology and I have pursued this theme in an experimental context (Love and Raff 2006).

the criterion of organization involves considering activity-function in the context of causal roles because hierarchically interconnected interdependencies are relevant to systemic capacities to which activity-functions make a contribution.[12]

Analyses of these interdependencies among functional elements are situated in methodological approaches from disciplines like functional morphology (Dullemeijer 1981; Schwenk 2001). For example, Lauder (1994) investigated jaw muscle activity patterns as homologues of function in fishes. Although individual muscle firing in the jaw contributes to overall feeding mechanics (a system capacity), each of these specific 'component' activities must be treated individually because of their compensatory and synergistic interactions (similar to that observed in *Hox* genes). The contribution of a particular muscle activity is dependent on the overarching organization of feeding mechanics such that the same activity may be playing a very different causal role or a dissimilar activity may play the same causal role (cf. Nishikawa et al. 2007). Functional anatomy in medicine provides further examples relating activity to causal role (Johansson et al. 2005). The activity of food transport in the alimentary system (digestive use-function) and the activity of gas transport in the respiratory system (respiratory use-function) are both facilitated by the oropharynx (back of the throat). The heart structure and activity of beating play functional roles in both the circulatory and respiratory systems that are not isomorphic. Hierarchy is also present; capillary diffusion is an element of the blood vessel system, which is an element of the vessel system (blood + lymphatic), which is an element of the circulatory system. Multiple activities contributing to the same capacity are also possible. The appropriate construal of function for seeking a correspondence across taxa is activity not causal role, because homologues appear under every variety of form and use-function and a causal role interpretation involves a particular variety of use-function. But the causal role account is relevant to identifying activity-function homologues through the criterion of organization.

Assessments of putative activity-function homologues organized into interconnected dependencies in the context of use-functions often involves reliance on structural information, such as muscle morphology and tendons connected to bone underlying a contractile activity. The relationship between form and function is asymmetric in that structures have an epistemological priority in the decomposition and investigation of biological activities (Dullemeijer 1981). This is especially salient in the historical record treated by paleontology where skeletal structures are more prevalent and the univocal determination of functions in extinct animals is difficult (Lauder 1995). Organization, as a criterion of activity-function homology, exhibits this asymmetry because ascertaining functional interdependencies usually requires attention to structural constitution and organization. This is consistent with the claim that determining homology of function does not require explicit connections to particular homologies of structure—activity-function homology may be recognized with or without correlated homologies of structure (Greene 1994; Lauder 1994, 1995; Wenzel 1992).[13] But the individuation of activity-functions relevant to homology is broadly

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[12] This is also congruent with the argument that non-arbitrary individuations of causal role functions are secured by ascribing them only to systems exhibiting hierarchical organization (Davies 2001, ch. 4).

[13] Some candidates for activity-function homology are directly tied to particular structurally homologous features, such as homeodomain DNA sequence and the activity of DNA binding. A different asymmetry between structure and function arises in phylogenetic reconstruction, which leans heavily on structural data (e.g. skeletal anatomy or DNA sequences), even though activity-function character states can also be scored (i.e. functional characters can provide good phylogenetic data). This is a result of the greater difficulty in obtaining functional data as opposed to structural data (Lauder 1990). The dependence of homology of function on structural characters in this sense is *indirect*, mediated through the identification of structural synapomorphies required to construct a necessary but insufficient phylogenetic context.

'structural' in the sense that they are treated as components in or aspects of organized biological systems, and is commensurate with biological practice in comparative studies that pick out functions as activities.[14] When use-functions are considered, causal role receives far more attention than viability or selection history (Amundson and Lauder 1994).

Philosophical consequences

The above account of activity-function homology is pertinent to three broad philosophical domains: (1) the analysis of functional characters such as behavior or psychological categories in philosophy of mind and psychology; (2) functional ascriptions and the diversity of reasoning practices in biological science; and, (3) causal generalizations and inferences made from model organisms in experimental biology. I will not discuss (1) because the topic is treated elsewhere (Ereshefsky, this issue; Griffiths 1997, 2007; Matthen, this issue; Wenzel 1992). Suffice it to say that my position grounds the argument for analyzing psychological categories in terms of homology and gives a specific, systematic account of what this means in the broader context of biological theorizing. It also allows the probing of more tendentious applications, such as whether cultures or cultural units can be homologous (Boyd et al. 2005 [1997]). I will only briefly touch on (3) toward the end because it demands independent discussion. The primary area where specific consequences will be teased out is (2)—functional ascriptions and the diversity of reasoning practices in philosophical accounts of biology.

While I have not argued for or against a particular view of function, my position puts a priority on comprehending actual biological reasoning and the theoretical relevance of different characterizations of function (Davies 2001; Wouters 2003, 2005). It is a form of functional pluralism rather than monism (cf. Neander 2002). Without embracing the heterogeneity of functional ascriptions, an appropriate sense of function for homology that was congruent with existing theoretical commitments could not have been recovered. The core objection to my account arises from a monistic perspective on biological functions. If the goal is to isolate "a unitary phenomenon that lies behind all the various sorts of cases in which we ascribe purposes or functions to things" (Millikan 1989: 293; cf. Neander 1991), the preceding discussion will be problematic. The use versus activity distinction as applied to homology specifically eschews understanding function in terms of use (whether selected effect, viability, or causal role). Instead of adjudicating criteria of adequacy for philosophical accounts of function, I want to focus on how a narrow understanding of functional ascriptions as selected effects encourages the mischaracterization of reasoning practices in biology, especially those related to homology.

An understanding of function solely in terms of natural selection is observable in Alex Rosenberg's recent discussion of reductionism.

> To call something a wing is not to describe it in terms of its composition, or structure, but in terms of the effects of something's having a wing: but which effect? Obviously, the effect of flight! Among all the many effects of having a wing, the one which confers its function, flight, is the one selected for because it and/or its

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[14] The success of activity-function homology is due in part to treating activities structurally ('structure'=*df* "The mutual relation of the constituent parts or elements of a whole as determining its peculiar nature or character"; OED). I am intentionally skirting the ontological issue of whether there are both entities (structures) and activities (functions) or, alternatively, whether activities can be reduced to the interactions of entities (cf. Tabery 2004).

> precursors was an evolutionary adaptation. …Biology "taxonomizes" the phenomena in which it interests itself functionally, not structurally. …Consider, for example, the claim that the homology/homoplasy distinction requires neutrality on whether etiology individuates a kind or not. Of course, the selected effects account of analysis [*sic*] doesn't commit its exponents to any particular etiology, only to the generic claim that each item in biological taxonomy has some etiology or other (Rosenberg 2006: 18–19).[15]

Our earlier discussion demonstrates that Rosenberg is mistaken in these claims about function, homology, and individuation. To call something a wing (or a tetrapod limb) is often, if not primarily, accomplished in terms of composition and structure (Amundson and Lauder 1994). And when function does play a role in individuation, it is usually in terms of activity or causal role, not viability or selected effect. This is precisely what makes comparative biology across large phylogenetic distances possible. Structures and activity-function homologues are traceable (in the sense that correspondences can be established) under every variety of form and use-function. Structural biology does not denigrate etiological aspects of biological phenomena; it simply treats them as orthogonal in its methodology.[16] More specifically, Rosenberg's rebuttal with respect to homology will not work. For if no particular etiology for a trait is in view then one cannot individuate anything. If biology taxonomizes 'functionally' (i.e. in terms of selected effect), then it requires a specific selection history *in advance* in order to accomplish its classificatory individuations. How does a functional morphologist individuate activities without any reference to a specific etiology? An over-reliance on selected effect function alone misconstrues biological reasoning (and is arguably not even coherent). Structural biology (inclusive of activity and causal role function) and homology take priority in character individuation (Griffiths 2006). This priority emerges from the fact that the establishment of homologies and individuation of characters are achieved independently of deep theoretical commitments about specific selection histories (see Griffiths, this issue, for discussion).

One response open to Rosenberg is to claim that the individuation of adaptations (i.e. selected effects) maps directly onto structurally individuated homologues. But this requires demonstrating that these individuations are equivalent, which is *prima facie* implausible because there are many reasons why they will not be isomorphic. Comparative, experimental, and structural biology are able to effectively utilize structure and activity-function individuated homologues without any reference to selected effect. Once we consider 'component' activities like individual jaw muscle firing patterns along with compensatory interactions in the context of a larger system ('organization'), this point is even more poignant because individuations using different concepts of function along with structural considerations can be quite divergent. Functional and structural individuation can be decoupled and are more likely to exemplify divergence when disparate hierarchical levels are considered.

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[15] "Every biologically interesting structure is labeled by the term that expresses its selected effect; how a structure is 'individuated'—how the border between it and other structures in the same animal or plant (or fungi) are drawn—depends on its selected effect, its function" (Rosenberg 2006: 137).

[16] "Amundson and Lauder and perhaps also Griffiths seem to maintain that there are not functional categories of any scientific significance in biology, with the exception of the analogous categories being categories of traits that have evolved independently to serve the same function" (Neander 2002: 391). This is a strange assertion because all three of these authors clearly state that causal role functional categories are ubiquitous in experimental biology. Only selected effect functional categories are identified with evolutionary analogies, which follows the mainstream neo-Darwinian tradition.

If it is a criterion of adequacy that philosophical accounts of biology explicate widespread reasoning patterns and illuminate their operation, then Rosenberg's perspective fails to do justice to comparative, experimental, and structural biology, all of which motivate the above account of activity-function homology. Large chunks of biology (past and present) simply do not make sense unless one admits the structural individuation of at least some (if not most) kinds. For example, the resurgence of interest in non-homologous features, such as parallelism (morphological convergence facilitated by homologous developmental pathways) or atavism (reappearance of a trait in some individuals that was ubiquitous in an ancestral species), is completely missed from this perspective (e.g. Hall 2003). These phenomena require more than etiological individuation since homologous developmental pathways must be distinguished from analogous ones in the case of parallelism and there is no selection history for an atavistic character. An adequate account of the nature of biological science cannot ignore or eliminate scientific practices without substantive qualifying explanation. Besides exemplifying the confusion about individuation, Rosenberg's brand of reductionism requires distinctions (such as functional versus molecular biology; Rosenberg 2006: 25), which evaporate when function is not equated with selected effect (cf. Love, in press). As a consequence of not capturing key aspects of reasoning in these areas of biology, Rosenberg's account of biological explanation is highly problematic.

One difficulty Rosenberg and others have is the inability to recognize the multiplicity of representational schemata in biology. Traits can be individuated using different criteria, including both structural and functional (use or activity) strictures, and these individuations are usually not translationally equivalent (Wagner 2001). Another difficulty is that criteria of individuation are assigned different ordinal relations of priority depending on the explanatory goals of biologists (Brigandt 2003). Finally, the ability to test individuation claims (methodology) motivates keeping selected effect function out of the conceptual foundations of homology. Evolutionary explanations require both pattern and process components. If individuation is accomplished in terms of selected effect functions, then a preferred causal factor (selection) is smuggled into the phylogenetic pattern to be explained, a classic example of adaptationist bias. Although every reconstructed pattern must make assumptions about process, the aim is for these to be minimal (populations of organisms are genealogically connected) rather than substantive (the major factor shaping populations of organisms is natural selection). 'Structural' individuations (inclusive of activity-functions) in evolutionary biology reflect hallowed epistemic goals thought to be characteristic of science, such as the independence and variety of evidence in hypothesis testing (cf. Griffiths 2006, this issue).

The final philosophical consequence of activity-function homology, which bears on causal generalizations derived from model organisms, can only be dealt with in a perfunctory fashion. Activity-function homology serves as part of the basis for making causal generalizations from model organisms in experimental biology to other less studied or unstudied organismal contexts. Although there are interpretive issues about the relationship between causation and activities (Tabery 2004), activity-function homology directs our attention to the stability or conservation of activities. This conservation, which requires a phylogenetic context in order to be established, is indicative of when the study of processes in model organisms will produce robust and stable causal generalizations. The widespread use of functional homology (legitimate *and* illegitimate) in molecular and developmental biology is aimed at exactly this kind of question, which explains its persistence in experimental biology despite conceptual ambiguities. But the requirement of a phylogenetic context also takes into account the criticisms of model organisms offered by evolutionary researchers (e.g. Hanken 1993). It has already been argued that experimental biology utilizes causal role rather than selected effect functions (Weber 2005). Activity-function homology adds a missing component to our understanding of these forms of reasoning. For example, generalizations concerning molecular signaling cascades (e.g. the *Wnt* pathway) are underwritten by the biochemical activities under scrutiny, not the developmental roles (though sometimes they coincide). Thus, activity-function information about a signaling cascade gleaned from model organism analysis can be generalized to other unstudied organisms even if the developmental role varies for the activity-function. Additionally, this allows an interesting conceptualization of signaling cascades that are put to diverse use-functions within the same organism: they are *serial* activity-function homologues, the functional equivalent of repeated structural units like vertebrae.

Conclusion

A variety of issues pertaining to homology of function remain to be considered. One traditional criterion for structural homology is 'special quality', such as a unique histological signature (cf. Ereshefsky, this issue; Griffiths, this issue). In some cases it might be argued that a special quality used to determine structural homology is itself an activity-function homologue (e.g. Nozaki and Gorbman 1992). My analysis provides a point of departure for considering how to treat these cases where the line between homology of structure and function is fuzzy. There are also linguistic issues that require attention. To what degree are the phrases 'functional conservation' or 'evolutionarily conserved function' synonyms for 'homology of function'?[17] In some cases, the terminology of "functional homology" is not used but the authors are interested in a phenomenon that could be described as such. "There is also an intimate relationship between the immune and metabolic response systems that has many evolutionary underpinnings …the functional units that control key metabolic and immune functions in higher organisms have evolved from common ancestral structures" (Hotamisligil 2006: 861). Another area that requires investigation is what it means to be a 'functional unit' (cf. Schwenk 2001), a question that intersects with ongoing discussions of modularity in development and evolution (e.g. Schlosser and Wagner 2004). Finally, how does the introduction of activity-function homology affect other concepts, such as analogy? Activity-function analogy appears confused because the invocation of analogy involves explicit appeal to selected effect (use) functions. But if we recall that activity-functions are a kind of 'structure', then we can retain the use versus activity distinction in a characterization of analogy: analogous activity-functions are *similar* by virtue of selection processes favoring comparable use-function outcomes.[18] Regardless, all of these issues necessitate further inquiry.

Although the very idea of functional homology is conceptually problematic, a legitimate concept of homology of function can be isolated by understanding function in terms of activity (what it does) rather than use (what it is for)—the same *activity-function* in

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[17] "We investigated functional conservation among the *Drosophila* zinc-finger homeodomain protein 1 (*zfh1*) and its mouse functional homologue Smad-interacting protein 1 (*SIP1*)" (Liu et al. 2006: 683).

[18] Vertebrate lens crystallins could be used to explore some of these issues (Piatigorsky 2007). The enzymatic activity of aldehyde dehydrogenase in different taxa can be activity-function homologous but its role as a transparent, refractive globular protein in the eye usually is not. This is because different metabolic enzymes (e.g. transketolase) and stress protection proteins (e.g. heat shock) were recruited into the role of lens crystallins in different vertebrate taxa because they also could play the role of a transparent, refractive globular protein, and thus lens crystallins as a class are most likely to be activity-function analogues.

different animals under every variety of form and *use-function*. Previous authors have recognized that selected effect interpretations of function are inappropriate for studies of homology in functional morphology (Amundson and Lauder 1994), but the ancient distinction between use and activity shows that causal role functions cannot be used to characterize homology of function because they concern a particular variety of function. The resulting conception of homology of function in terms of activity is valuable because of the three distinct motivations highlighted at the outset: prior studies of behavioral homology, widespread use in molecular developmental genetics, and the connection with evolutionary innovation. Exploring activity-function homology in the context of molecular developmental genetics (‘experimental biology’) demonstrates its usefulness and identifies the complexity arising from different aspects of hierarchy in biological systems. A phylogenetic context is necessary but insufficient for activity-function homology, and organization, in the sense of hierarchically interdependent dependencies (similar to relative position and connection among skeletal elements), is a promising criterion for guiding the identification of correspondences among activity-functions. The criterion of organization also reveals a distinct place for the causal role interpretation of function in reasoning about homology used in functional morphology and allied approaches.

Activity-function homology has philosophical implications for the study of behavioral and psychological categories, our comprehension of biological reasoning and functional ascriptions, and the basis of causal generalizations derived from the study of model organisms. The disciplinary nexus from which it emerges (comparative, experimental, and structural biology) suggests that existing epistemologies of biology built from the theory of natural selection alone (especially selected effect function) are inadequate. Philosophical accounts of scientific knowledge cannot lose contact with actual scientific practice and the analysis of activity-function homology is explicitly motivated by this kind of criterion of adequacy. The ‘principle of natural selection’ is not as central to every explanation in biological science as some think and Dobzhansky’s famous slogan (‘nothing makes sense except in the light of evolution’) is not just about adaptation and selection—descent with modification matters too. Additionally, activity-function homology provides a conceptual bridge between evolutionary theory and experimental biology, which is critical to ongoing attempts at synthesizing evolutionary and developmental biology. In order to genuinely encapsulate the epistemological heterogeneity of biology, we need to devote more attention to how biological knowledge is actually structured, as well as rethinking the nature of evolutionary theory in a broader sense than is understood by many philosophical commentators. An overly narrow view of functions and ignorance of diverse conceptual practices in biology should no longer obscure our attempts to elucidate the dynamics of reasoning and explanation in biology. It is in this sense that ‘homology of function’ is a biological concept with philosophical consequences.

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