

What Is "Homology Thinking" and What Is it for?

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ABSTRACT

In this paper I examine the thesis by Marc Ereshefsky that, in evolutionary biology, there is a third style of thinking, besides the well-known "population thinking" and "tree thinking." Ereshefsky proposes "homology thinking" as a third approach, focused on the transformation of organismal phenotypes. In this short commentary, I aim at identifying the underlying biological assumptions for homology thinking and how they can be put to work in a research program within evolutionary biology. I propose that homology thinking is based on three insights: 1) multicellular organisms consist of developmentally individualized parts (sub-systems); 2) that developmental individuation entails evolutionary individuation, that is, variational quasi-independence; and 3) these individuated body parts are inherited, though indirectly, and form lineages that are recognized as homologies. These facts support a research program focused on the modification and origination of individuated body parts that supplements and puts into perspective the population genetic and phylogenetic approaches to the study of evolution. *J. Exp. Zool. (Mol. Dev. Evol.)* 9999B:XX–XX, 2015. © 2015 Wiley Periodicals, Inc.

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Different approaches to the study of evolution have been characterized as different "styles of thinking." The most prominent ones are "population thinking" (Mayr, '59) and "tree thinking" (O'Hara, '97). Population thinking recognizes that the unit of evolutionary change is the population, that is, the demographic unit in which genetic variation competes for representation in the next generation and thus has the potential for evolutionary genetic change. This is the dominant approach for explaining adaptation and the origin of species. In contrast, tree thinking is underlying the comparative study of biological diversity. It recognizes that species are, in most cases, not statistically independent instances, like experimental replicates are in the best of circumstances. But rather, species are connected in a hierarchical structure through their phylogenetic history.

In recent years, a third style of thinking has been proposed in biology, namely that of "homology thinking" (Ereshefsky, 2012). Ereshefsky defines homology thinking as "an approach to understanding biological phenomena that focuses on the historical nature of homologs. Homology thinking explains the properties of a homolog (or a range of properties among a homologs's character states) by citing either an initial condition or a series of events in the history of a homolog" (p. 397 in Ereshefsky, 2012). Interestingly, the notion of homology thinking arose not in evolutionary biology per se but rather was put

forward by some evolutionary approaches to behavior and cognition (Griffiths, '97; Matthen, 2000; Ereshefsky, 2007; Matthen, 2007) and more recently is used in evolutionary linguistics (Balari and Lorenzo, 2013, 2015), even though the homology concept of course arose in the comparative biosciences (see [Panchen, '94] for a short history of the concept). Never the less, in 2012 Marc Ereshefsky made a strong argument for the utility of homology thinking in biology in general, concluding that homology thinking leads to a richer and deeper understanding of biological phenomena than adaptationist/functionalist explanations (which Ereshefsky called "analogy explanations"). Of course adaptationist explanations have their

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role in evolutionary biology and beyond, but refer to relatively general attributes of organisms that are most directly related to functional performance and fitness rather than the mechanistic structure of the organisms themselves.

Introducing a third perspective on evolutionary processes is not only a complication to accommodate the complexity of organismal evolution, but also has its conceptual benefits (Griesemer, 2006). A dyadic structure with two theoretical perspectives, say population and tree thinking, has a tendency of leading to polarization. Each perspective has its own agenda and there is very little that can be said from each point of view to assess the relative importance of the other. In contrast when we have three theoretical perspectives any two of them can be viewed from outside their relationship, namely from the theoretical commitments of the third perspective. That fact can help ease the tendency for polarization among ideas. Specifically, consider the relationship between population thinking and homology thinking, which can be construed as antagonistic (Amundson, 2005). The relationship between them can be reconciled from the tree thinking perspective by relating the outcomes of population genetic processes in phylogenetic history. The models of population biology have no historical depth and that of homology thinking lack grounding in population genetic mechanisms. Only with tree thinking the immediate population genetic mechanisms can be connected to the macro-evolutionary outcomes of evolution, those captured in research based on homology thinking. Similar arguments can be constructed for the two other relationships, tree- and homology thinking, as well as tree- and population thinking. In either case it is easy to see that the presence of the third perspective also adds to the productivity of the research agendas.

In this brief commentary, I want to expand on Ereshefsky's approach and explain what homology thinking can mean for biology from the perspective of a developmental genetic approach to homology (Wagner, 2014). Homology thinking also plays a role in the study of culture and human behavior (Griffiths, '97; Balari and Lorenzo, 2015; Tomlinson, 2015), but I will limit my remarks to the study of biological evolution.

THE ELEMENTS OF HOMOLOGY THINKING

Different "styles of thinking" are characterized by reference to some biological facts that are perceived as fundamental for the study of evolution. These facts are then used as starting points for the interpretation and analysis of a broad set of phenomena. For instance population thinking recognized that, at the micro-level, evolution proceeds through the introduction of genetic variation, and the filtering of this variation through various population biological processes (random drift, selection, meiotic drive, etc.) depending on population size, fitness differences and mating- and population structure. Population thinking is then applied toward a wide variety of biological phenomena seeking explanations through the lens of population genetics. Given

that background, what are the biological facts that are perceived as fundamental for homology thinking?

Homology thinking is based on the realization, though often implicit, that organisms consist of sub-systems (modules, body parts etc.) that are developmentally, variationally and functionally individuated. If we focus on multicellular organisms the most fundamental kind of sub-systems are different cell types. Even the most simple free living animal (metazoan), *Trichoplax adhaerens*, which has no anatomical organs, consists of at least five cell types (Grell and Benwitz, '71; Syed and Schierwater, 2002). Without doubt, the cell types of *Trichoplax* are dedicated to different (sets) of functions and likely have genetic individuality analogously to that found in the cell types of mammals, insects, and nematodes (Wagner, 2007; Arendt, 2008; Graf and Enver, 2009; Hobert, 2011). That is, each cell type executes a different genetic "program" that leads to different developmental and physiological outcomes in different cell types.

A corollary to genetic and developmental individuation is (partial) evolutionary individuation. As each cell type can, in principle, differentially regulate sets of genes from the same genome, mutations can have different phenotypic effects on different cell types. That is, developmental genetic individualization entails the possibility that different cell types are affected differentially by mutations to the genome and thus can have different evolutionary histories. Developmental individuality entails evolutionary individuality, and thus developmentally individuated cells are recognized as homologous cell types across species.

The opposite implication is also true, without developmental individuation there is no evolutionary individuality of the cell type and it can not be recognized as a different entity. Only cells that execute different differentiation programs can look different and adapt to different functional needs. To identify in different species individual cells among a set of cells executing the same genetic program, is not only difficult but it is also biologically meaningless. To identify a cell across different species implies that the cells are developmentally individualized (Wagner, 2014). The same argument can be constructed for multicellular organs, like brains, eyes, and livers (or insect wings, and nematode vulvas for that matter): *developmental genetic individuality entails evolutionary character identity*.

The evolutionary individuality of body parts, in turn, is what is recognized as homology of body parts across species. This observation leads us to the next element of homology thinking, and that is the recognition that individualized body parts tend to be inherited between generations, at least at the phenomenological level, which means that they are either recreated in each generation and thus form a lineage, or are recreated in a regular trans-generational pattern as in the case of complex life cycles. *Homologs form lineages and have phylogenetic continuity*.

One has to recognize, though, that the way that body parts and cell types are inherited is much more indirect than that of genes

(see [Wagner, '89] and others). In the case of genes there is a direct copying action leading to two sister DNA strands, each of which even contains one half of the parental DNA molecule. That is in DNA replication there is even material overlap between the parental and the descendant copy of genetic information. For all other characters the pattern of inheritance is more indirect. Cell types, organs and even the obligatory associations with micro-organisms have to be recreated by other means (Pradeu, 2012), largely through a developmental pathway. Nevertheless the robust trans-generational recreation of these parts and associations leads to what can be described as a lineage of descent, due to the reliable re-instantiation of a physical unit in consecutive generations (see also Suzuki and Tanaka, presentation at the ISHPSSB meeting in July 2015, Montreal, Canada).

To summarize, homology thinking is based on three related insights, namely that organisms consist of

1. sub-systems that are individuated from the rest of the organism in terms of development, genetic variation and function, and that
2. developmental individuation entails evolutionary individuation, and finally that
3. these subsystems (characters) are inherited between generations, though indirectly, and thus can be identified across individuals of the same species, and among different species, traditionally called homologs.

If we accept these premises, one important consequence follows for the study of organismal evolution. This scheme allows for three distinct modes of evolutionary change: 1) the modification of existing characters (changes in character states); 2) the origin of a novel body part (novel character identity, aka Type I novelty, see Wagner 2014); and 3) the loss of a character (character reduction, rudimentation or loss). A detailed discussion of these modes of evolution can be found in Wagner (2014).

WHAT ARE THE BENEFITS OF HOMOLOGY THINKING?

Adaptationist models of biological evolution have a tendency of reducing the biology of an organism to a few quantitative variables. In the most extreme cases, the phenotype of an organism is represented as a number on a one dimensional scale, fitness. Frequently one can hear researchers saying that "the only biologically relevant character is fitness." Fitness in itself, however, is difficult to measure and in many empirical studies is replaced by a small number of so-called fitness components, like age at reproduction, fertility and survival rate (Stearns, '92). And even when an evolutionary biologist studies specific parts of an organism the objective is to measure the attribute that is most strongly correlated to fitness, that is, the "performance" of a character in doing a certain function (Arnold, '83).

Although the study of adaptation along the lines sketched above has yielded and continues to yield important and even

surprising insights, as for instance in genomic conflict theory (Haig, '93), it nevertheless is committed to a rather abstract picture of the organism. Organisms are reduced to points in an abstract space of quantitative variables assumed to influence fitness, and the life of the organism is vaguely captured by a numerical function, the genotype to fitness map. The fitness function describes how selective forces push a cloud of points around on the adaptive landscape (Lande, '79). Mechanistic models, that dominate the rest of biology, hardly fit in this rather abstract picture of biology.

The approach suggested by "homology thinking," in contrast, starts out with the insight that organisms are complex, mechanistically integrated, and structurally heterogeneous systems. The structural heterogeneity of organisms is acknowledged by identifying individualized parts or sub-systems with historical continuity, that is, homologs. Evolutionary change is then understood as the modification and the transformation of a complex, integrated system made possible by the mutations that affect the mechanisms of development, physiology, and reproduction. The mechanistic structure of the organism is the starting point and central concern of the research program that follows this style of thinking rather than a complication to be abstracted away.

Applying this approach to specific evolutionary events and episodes requires first to learn as much as possible about the structure and function of the ancestral state from which the derived state (the explanandum) evolved (Larsson and Wagner, 2012). This can be achieved either by ancestral state reconstruction based on the comparative method (Felsenstein, 2003), or, to a limited but increasing extent, through the physical realization of the ancestral system (e.g., ancestral proteins; Thornton, 2001; Bridgham et al., 2009). The purpose is to understand the starting point and the mechanistic possibilities that existed before the transformation ensued. What subsystems existed in the ancestral organisms? What were their developmental and functional "norms of reaction"? A model of the ancestral state is necessary to investigate how the evolutionary transformation was effected by mutations that modified the ancestral mechanisms.

Here is an example of how this style of thinking may be implemented in a specific case. It exemplifies the kind of questions and approaches to use in a research program based on homology thinking, not a list of final answers. The example concerns the evolution of mammalian pregnancy. Viviparity is a trait that evolved many times in vertebrate history, although the exact number is still under debate (Blackburn, 2015; Griffith et al., 2015; Pyron and Burbrink, 2015). Among the many examples of viviparity, the pregnancy of eutherian (placental mammals) is unique due to the nature of placentation (Mossman, '87). Only in eutherian mammals is pregnancy deeply invasive, involving the erosion of considerable maternal tissue and a direct interaction between the trophoblast and the maternal stroma (Wagner et al., 2014). According to ancestral state reconstructions

this trait evolved in the stem lineage of eutherian mammals, and has been reverted a few times after it evolved (Mess and Carter, 2006; Wildman et al., 2006; Elliot and Crespi, 2009). To understand the evolution of invasive placentation poses unique challenges, that go beyond the question whether and how nutrient and gas exchange is affected. Invasive placentation leads to the invasion of semi-allogenic cells into the body of the mother and to the partial destruction of maternal tissue. Pregnancy, thus, is very similar to disease processes, but is never the less tolerated by the mother. To realize this form of reproduction the uterine tissue has to undergo radical transformations in the way it reacts to the presence of a partially destructive implant (Swaggart et al., 2015). Morphologically invasive placentation is made possible by the origin of at least two novel cell types, the so-called decidual stromal cell (DSC; Gellersen and Brosens, 2014) and a special form of uterine immune cell, the uterine natural killer cell uNK. The DSC develops from a fibroblast like stromal cell, the endometrial stromal fibroblast (ESF). From the perspective of homology thinking the problem is to understand where the maternal system of fetal accommodation comes from and how the ancestral cells were transformed during the evolution of eutherian pregnancy. Do mammals without invasive placentation, for instance marsupials, have decidual cells or ESF? Where do ESF come from and what where the molecular changes to allowed the origination of DSCs? Some answers are emerging. It was found that ESF but not DSC can be identified in the short tailed gray opossum (Kin et al., 2014), a derivative of the most basal branch in the marsupial tree (Freyer et al., 2003). Furthermore, ESF have a strong affinity to mesenchymal lymphatic cells, follicular dendritic cells (Kin et al., 2015). Given a hypothesis of how the cells that make invasive placentation possible we can ask what the gene regulatory network changes were that created this unique functional capabilities. That is, by reconstructing the phylogenetic (homological) relationships among tissues and cells constrains the search for functionally important and specific molecular mechanisms (Kin et al., 2015; Musser and Wagner, 2015). Of course this style of research is not limited to the evolution of mammalian pregnancy, but has examples in other areas as well. Well developed examples are the evolution of *Drosophila* sex combs (Kopp, 2011) and flower parts (e.g., Kramer and Irish, '99; Jaramillo and Kramer, 2007; Endress and Doyle, 2009; Specht and Bartlett, 2009; Melzer et al., 2010).

From the above example, it is obvious that what here is called “homology thinking” is closely allied with other fields of study, most notably that of evolutionary developmental biology (evo-devo, e.g., Carroll, 2008) and the so-called “functional synthesis” (Dean and Thornton, 2007). Evo-devo seeks to study the evolution of development as a means to understand the evolution of morphological phenotypes and to integrate developmental biology into evolutionary biology. The functional synthesis is a confluence of molecular evolution with experimental molecular biology. The trademark of the functional synthesis is the

molecular study on reconstituted ancestral proteins (Thornton, 2001). The goal is to understand which amino acid substitutions caused which effects on the function of the protein and how new molecular functions, such as new ligand binding activities, arose in evolution. Both, devo-evo and the functional synthesis, have a strong emphasis on molecular mechanisms similar to the brief outline of “homology thinking” above. Nevertheless, the program of “homology thinking” in biology has distinct attributes in its emphasis on an organismal perspective in which the individuated parts of the organism are central players in the explanatory narrative. This program aims at understanding the structure, organization, and function of organisms as the unit of biological existence. Furthermore homology thinking acknowledges that organisms consist of parts, each with their own developmental and functional capacities. Homology thinking then seeks to understand evolutionary change as the modification and transformation of these subsystems and their inherent norms of reaction. The final goal is to understand the developmental and functional organization of a derived organism from where it is coming from, the organization of the ancestral organism, and the sequence of gene mutations affecting the functioning of the cells that make up the organism.

So what are the benefits of homology thinking in biology? From the perspective proposed in this paper, homology thinking is the framework within which the mechanistic branches of biology (genetics, molecular and cellular biology) can most productively interact with evolutionary models to understand biological diversity. Homology thinking constrains both, the use of mechanistic models in evolutionary studies as well as the use of evolutionary inferences in molecular biology. The constraints imposed relate to the question which parts and processes can truly be compared across species, which is of primary importance in bio-medicine, where we study one species, for example, mouse, in order to learn about another, humans (Swaggart et al., 2015). The constraints also relate to the question how to “read” (interpret) inter-specific differences in mechanisms by putting them in a phylogenetic context. Neither tree nor population thinking can do that or have traditionally done that, because of their abstract representation of organismal structure and activities (as discussed above). Through homology thinking molecular biologists can learn to see the processes they study as the product of evolutionary transformations rather than as brute facts of nature, like the laws and regularities of physics and chemistry. And evolutionary biologists can learn, through the vehicle of homology thinking, to appreciate evolutionary change as the transformation of modular mechanisms, rather than limit themselves to tracing evolutionary changes of phenotypic outcomes.

CONCLUSIONS

Homology thinking is a style of research in evolutionary biology that complements population thinking (Mayr, '59) and tree thinking (O'Hara, '97). More than metaphorically, homology

The three-legged stool of evolutionary biology

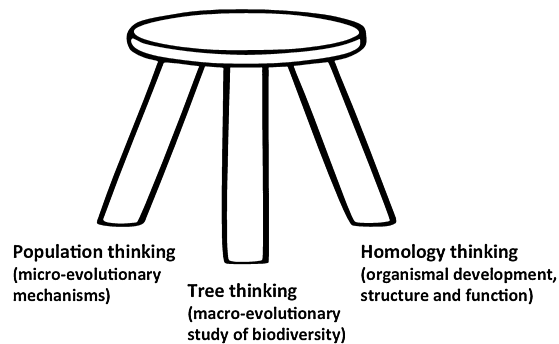


Figure 1. The "three legged stool of evolutionary biology." There are two styles of thinking recognized in evolutionary biology, population thinking and tree thinking. In this paper, I argue that Ereshefsky's notion of "homology thinking" complements the other two in adding an organismal perspective to the other two styles of research.

thinking is the third leg of the stool of evolutionary biology (Fig. 1). It adds an organismal perspective to the micro-evolutionary perspective of population thinking and the macro-evolutionary view of tree thinking. As such homology thinking does need the other two to be scientifically valid, and also puts the other two in perspective; as population and tree thinking puts homology thinking into perspective. The threeness of population–tree–and homology thinking has the potential to avoid unnecessary polarizations as each provides unique assets to the study of evolution.

Readers of Marc Ereshefsky's 2012 paper in *Biology and Philosophy* will appreciate that the outline of homology thinking here is a restatement of Marc's claim that homology thinking has the ability to provide more detailed and deeper insights into the processes and causes of evolutionary change than a functionalist perspective alone. Readers will also appreciate that Marc had broader applications of homology thinking in mind than are covered in this brief commentary. Homology thinking outside biology, for example, humanities as well as the behavioral and social sciences, needs to be developed by people who have a deep understanding of these domains of knowledge.

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