What's New

A Review of *The Origins of Evolutionary Innovations: A Theory of Transformative Change in Living Systems*.

By Andreas Wagner, Oxford University Press, 2011

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The Origins of Evolutionary Innovations is an important contribution to evolutionary theory. Using the novel concept of *genotype network*, defined as a set of genotypes with the same phenotype, and drawing on examples from the three “system classes” of metabolic networks, gene regulatory circuits, and RNA and protein molecules, Andreas Wagner describes a scenario in which populations of organisms perambulate along these networks, with their progeny potentially accessing, by small genetic steps, novel phenotypes heterogeneously distributed in the vicinity of the networks. The roles of robustness, plasticity, and genetic assimilation are considered, and a resolution of the neutralist-selectionist debate is proposed. It is suggested that extensions of the book's framework to incorporate niche construction and self-organizing processes (in the excitable condensed materials sense, not the graph theoretical sense the author considers), would advance its potential as a convincing alternative to the standard evolutionary narrative.

KEYWORDS

Phenotypic novelties • Genotype networks

This book is concerned with, and makes an important contribution to, answering the central question of evolutionary theory: By what mechanisms and processes do organisms undergo transformative change? Animals or plants may undergo alterations in morphology or activity during their lifetimes, but only if such alterations are conveyed to the next generation can they contribute to the establishment of new forms. Heritability by itself is not decisive: offspring can differ from their parents at a variety of genetic loci without this constituting evolutionary change, notwithstanding the fact that on theoretical grounds the standard model, stemming from the Modern Synthesis, asserts that any such variation represents incipient evolution (i.e., evolution is change in allele frequency). Clearly, some gene changes make more of an evolutionary difference than others. By placing *phenotype* at center stage and treating genotypes not in terms of their selective advantage, but rather with respect to the changes they exert on the phenotype, the author subtly but significantly reorients the explanatory terrain of evolutionary theory.

Andreas Wagner takes heritable qualitative alterations or additions to the phenotype – *innovations* – as the hallmark of evolutionary change. Referring to examples such as insect and bird wings, flowers, plant and animal vascular systems, teeth, silk, and multicellularity, he states that “Every macroscopic organism has

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visible traits that...changed not only organismal lifestyles, but also the future evolutionary path of life” (p. 1). Innovations can be precipitated by mutations, making them instantly heritable, or be induced by external influences and, if the conditions persist, subsequently become assimilated into the organism’s genome. A problem with the mutational route to innovation, at least with respect to the conventional narrative, is that if a character does not yet exist (many important ones having arisen without apparent precedent – e.g., arthropod segmentation, the vertebrate neural crest), it is difficult to see how it can be incrementally improved by natural selection (Müller and Newman 2005). But the latter scenario is precisely how evolution is supposed to occur: “macromutations” that bring qualitatively new characters into existence are anathema to the Modern Synthesis, which abhors saltation.

The assimilational route to innovation is also difficult to square with the standard model. Novel bauplans or structures that arise developmentally or conditionally during an individual organism’s lifetime, such as metamorphosis in insects and amphibians or polyphenisms in plants, are changes of the kind and scale seen during evolution. These are usually considered to be products of evolution rather than the raw material of innovation, however, owing to the general belief that most important characters are adaptations (Linde-Medina 2011); if something is in an organism’s phenotypic repertoire it must have been selected for at some point in the history of its lineage. But there is evidence to the contrary: the breaking of left-right symmetry (Palmer 2004) and menstruation in certain mammals (Emera et al. 2012) are only two of many traits for which evidence supports evolution by a “phenotype precedes genotype” scenario (see also West-Eberhard 2003).

Wagner seeks to overcome these apparent inconsistencies of the standard model. He primarily focuses on three classes of systems (a system being defined as “a set of elements or parts that cooperate to perform a task”; p. 5) he deems to be central to innovation: large metabolic networks, gene expression regulatory circuits, and macromolecules (proteins and RNA). He argues that “[m]ost innovations in macroscopic traits can ultimately be traced to...new metabolic pathways, new patterns of gene activity in regulatory circuits, and new molecules” (p. 5). The concentration on subsystems for which genotype-phenotype mapping is relatively straightforward leads to a somewhat overstated perspective on genetics as the primary causal element in innovation:

Innovations originate with a genotypic change whose effects translate into a phenotypic change. ...To produce evolutionary innovations, biological systems must explore many different phenotypic variants before finding one that may become an innovation. Such phenotypic variants are produced by mutations (pp. 4, 74).

This gene-centrism is moderated later in a chapter devoted to phenotypic plasticity, but the treatment remains solidly grounded in genetic causation. He alludes to the evolutionary significance of complex morphological and behavioral traits, but argues that much more is understood about the relation between genotype and phenotype in his chosen subsystems, and mounts his case for a reconceptualization of the origins of innovation in these circumscribed arenas. In this he is largely successful, though he frankly notes that some of the key questions about evolutionary innovation reside precisely in the domains he has set aside.

The conceptual framework Wagner uses to explore genetics-based innovation is the *genotype network*. Not to be confused with the similar-sounding and widely used “genetic network” (which Wagner calls “genetic circuit” or “regulatory network”), genotype networks are defined as sets of genotypes that have the same phenotype (p. 14). Although this idea is related to what other theorists have termed “neutral networks,” Wagner argues for a distinction that ultimately supports his de-emphasis of natural selection’s role in innovation (p. 15). Each genotype is a point in a high-dimensionality space in which the coordinates are related to the “values” (e.g., alleles) that the component genes can assume. Any metabolic, regulatory, or molecular system will reside at a point in the corresponding space, and random genetic change will allow the ensemble of organisms incorporating these systems to perambulate through it. The existence of genomic networks thus permits the population of organisms to sample many genotypes without changing their phenotypes. Genotypes specifying novel phenotypic departures from the network’s associated phenotype, moreover, will be differentially accessible from various sites in the network.

This idea undermines conventional thinking about the evolutionary process, since it postulates a world in which useful innovations are often a short genetic step away from a well-established phenotype. Although much of the author's own work is computational in nature, using fairly abstract models, the book is filled with many carefully explained examples from empirical and experimental literature that support the contention that genotypes specifying novel functions or structures in the three chosen system classes are often one or a few mutations away from the current population mean for a selected trait. The evolution of hemagglutinin, a key virulence factor of human influenza virus, is characterized by episodes of small genetic changes with large effect on the antigenic phenotype alternating with periods of time where genetic variation accumulates with little phenotypic change (p. 101). This is well accounted for in Wagner's genotype network model, where population members (viruses in this example) wander for varying amounts of time through a genetic space of constant phenotype, with some individuals breaking through to an adjacent site, linked to a different genotype network with a distinct phenotype, having a novel functionality suitable to new conditions.

The genotype network concept challenges the cut-and-dried distinction generally made between deleterious, beneficial, and neutral mutations, suggesting instead that the capacity of a population to wander through a genetic space of constant phenotype can place the identical gene alteration into any of these three categories, depending on ancillary gene changes consistent with the same phenotype. Different sites in a given genotype network, moreover, will have as neighbors different novel phenotypes. This point is driven home with additional examples of molecular evolution, as well as numerous ones from metabolic and regulatory circuit evolution.

Robustness, the resistance of a system to changes in phenotype in the face of environmental or mutational change (the subject of a previous book by the same author; Wagner 2005), promotes evolutionary innovation in this picture, since it increases the size of a genotype network and thereby affords accessibility to more novel phenotypes. Additionally, the likelihood that a mutation is deleterious is smaller for populations with more robust phenotypes. A discussion of the multiple effects of gene duplication in enhancing robustness, enlarging genotype networks, and capitalizing on novel phenotypes once they are encountered demonstrates the power of this approach (pp. 128-31).

Niche construction (Odling-Smee et al. 2003) is a concept that would seem highly relevant to the book's conceptual framework, but it is barely touched on. In the standard model, increasingly better adaptations to pre-existing environmental niches, or the presence of variants that are fortuitously beneficial in changing environments, drive evolutionary change. The genotype network formulation helps in both respects, because the postulated repository of variation enhances the probability of breakthrough optimizations and productive response to new challenges. It is equally possible, however, that a novel phenotype accessed from a genotype network will lead to a subpopulation of organisms that establish themselves in an entirely independent niche. The adaptive gradualism of the Modern Synthesis, where the substantial departure of a character from the population's mean phenotype requires many cycles of selection, is less compatible with this kind of scenario than is Wagner's model, where the appearance of novel forms can be relatively sudden. Indeed, the author's problematization of the notion of fitness in his discussion of the neutrality vs. selection controversy (p. 95) hints at a tacit departure from the adaptationist paradigm that is, however, in little evidence elsewhere in the book.

An expansion of the book's theoretical framework to include non-genetic determinants of phenotypic variation first comes in a discussion of stabilizing and canalizing selection; i.e., selection that "disfavors variants of a population's current phenotype, whether they arise through rare genetic perturbations, or through more frequent non-genetic perturbations (such as the incessant perturbations caused by thermal motion in protein and RNA molecules)" (p. 162). Wagner's claim that, "it is these processes that are fundamentally responsible for how genotypes map onto phenotypes" (pp. 162-163), suggests an evolutionary regime that preceded the modern-day one in which populations can comfortably navigate genotype networks of constant phenotype. Further, he speculates that "plasticity is almost certainly a primal feature of life" (p. 181). Although the author does not take this point further, such primitive plasticity in ancestral, pre-canalized forms implies that environment-dependent innovation may have been more important early in evolution than it is in present-day organisms (see Newman and Bhat 2009).

Wagner provides instructive examples of micro- and macro-environmentally dependent phenotypic plasticity at a number of organizational levels—including from the system classes he has chosen as paradigms of genetic determination of phenotype—and discusses the conditions under which such changes may become assimilated into the organism's developmental repertoire, thereby contributing to evolutionary change. For example, he describes the interconversion of proteins such as the cytokine lymphotactin between different global conformations and the catalytic promiscuity of enzymes such as chymotrypsin (pp. 174-175).

The fluidity of genotype-phenotype mapping goes even deeper than described, however. More than 30% of eukaryotic proteins are intrinsically disordered or unstructured (Radivojac et al. 2007), assuming their functional conformations in a context-dependent fashion. Different rates of mRNA translation, which can be influenced by environmental factors such as temperature (Zhang et al. 2009), can cause proteins with the same sequence to have different folded shapes and functional roles (Kimchi-Sarfaty et al. 2007). Apart from the qualifications these phenomena place on classic notions like Anfinsen's thermodynamic hypothesis and Crick's Central Dogma (Newman and Bhat 2007), they complicate the postulate of sets of genotype networks that have a conserved phenotype. Wagner asks "Does plasticity facilitate adaptation?" (p. 181), but perhaps this is too narrow a question. As Richard Lewontin has long emphasized, the dynamicity and reciprocity of phenotypes and niches undermine any rigid notion of adaptation (Lewontin 2000). This is another case where it seems that the book's critique of evolutionary theory (implicit in its alternative framework) can be pushed even further.

Changes in metabolic systems, gene regulatory circuits, and varieties of molecules across organismal lineages are certainly evolution, but they were not the phenomena that mainly engaged the theoretical efforts of Darwin and Wallace, nor are they the sort of things that rile creationists. Macroevolution, the contentious part, is associated with morphological disparity, but the mechanisms generating form are not a primary focus of Wagner's analysis. This can be attributed in part to the gene-centrism of his framework.

The phenotypes I have focused on in this book are simpler than macroscopic traits of higher organisms. What we can learn from them about such traits is limited; for example because they lack the spatial dimension of macroscopic traits. However...they are the building blocks of macroscopic traits (p. 160).

This is reiterated in the summary chapter: "New phenotypes in [the metabolic and gene regulatory network and protein and RNA molecule system classes] are the building blocks of innovation on all levels of biological organization, including the complex, macroscopic innovations in multicellular organisms" (p. 214). This seems to be a significant overreach. The toolkit genes of multicellular animals were largely present in single-celled ancestors but took on their specific developmental roles only in a multicellular context, when they came to mobilize physical processes pertinent to mesoscale systems (Newman and Bhat 2009). In the absence of these physical processes there is nothing in Wagner's three biochemical system classes that enable us to understand why animal embryos are multilayered, why arthropods and vertebrates are segmented, and why humans typically have five fingers. His contention that "[T]he dynamical change of gene activities caused by regulatory interactions...can capture important aspects of the dynamical complexity involved in pattern formation of development, such as static geometric patterns and travelling waves in the activities of regulatory molecules" (p. 160), is inconsistent with this system class's lack of a spatial dimension (which he notes explicitly).

Wagner asserts that "both natural selection and self-organization are equally necessary in evolution" (p. 91). This conclusion will be congenial to a growing number of evolutionary developmental biologists, since what they mean by self-organization is the inherent form-generating capabilities of complex, condensed materials such as cell aggregates and embryonic tissues. The author's use of the concept is entirely different. Considering the genetic space within which the numerous genotype networks having a constant phenotype exist, and using arguments from the general theory of random graphs, he shows that (insofar as the genotype networks have properties in common with such graphs) stipulating the fraction of a typical genotype's neighbors as "neutral" (i.e., having the same phenotype) between 0.1 and 0.5 is both necessary and sufficient for the existence of genotype networks that extend throughout (in technical terms, it forms a "percolating cluster" within) the entire space. Although this formal property of genotype networks falls within a general

definition of self-organization, it pertains to a virtual space of potential genomes that populations of organisms might explore, rather than the generative dynamics of actual developmental systems that have increasingly figured in models of morphological evolution.

Despite these few reservations, which mainly relate to Wagner not going far enough along the path he has laid out, I really enjoyed this book. There was hardly a page from which I did not learn something new in terms of biological facts or modeling strategies. Everything is explained in a lucid fashion with a graceful and self-reflective prose style. Abstractions and idealizations are not oversold and are presented alongside discussions of their limitations. It is difficult to imagine any future work on evolutionary innovation that does not take this volume as a touchstone.

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