A network of paths toward innovation

The Origins of Evolutionary Innovations

Andreas Wagner, Oxford University Press, 2011, ISBN: 978-0199692590 hardcover, 253 pages, price: 83 €.

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DOI 10.1002/bies.201200016

Any mention of neutral change and adaptation in the same breath inevitably brings to mind the battles over the causes of molecular evolution that have been so prominent and long-running in the field. While these arguments have evolved with the development of new models and new technologies, the central dichotomy has remained: beneficial changes, that fix because of natural selection and contribute to adaptation, are one thing, and neutral substitutions, that fix only by chance, are something quite different. Wagner has been a cogent and prolific advocate of a radical alternative: neutral variation within a population can provide an essential foundation for adaptive change. In experimental papers [1], numerous simulation studies, reviews [2], and his previous book [3], Wagner has emphasized how epistasis – interactions among genes that shape the adaptive consequences of mutations – allows neutral variation to modulate the effects of other mutations, producing a vast range of possible mutant phenotypes that may lead to an adaptive innovation.

Wagner did not invent the idea of neutral variation fueling adaptation, but he has done much of the hard work to translate the idea into the mainstream of biology. The early foundations of this idea came from the pioneering work of investigators who had trained as physicists and chemists, and applied biophysical ideas and computer models of macromolecules to evolutionary questions [4–8]. In his 2005 book *Evolvability and Robustness in Living Systems*, Wagner synthesized these studies with other evidence for neutral networks across a broad range of scales, drawing together the genetic code, macromolecular structures, regulatory and metabolic networks, and developmental systems. The magnitude of this evidence for degeneracy and epistasis, and of its implications for evolution, was exciting and influenced a broad audience. But Wagner stopped short of presenting a fully realized theory of how all this potential for neutral variation could explain the astounding ability of life to produce true innovation in the face of environmental change and opportunity.

In this new book, Wagner moves his focus from robustness to ''innovability'' – an evolutionary propensity to innovate – but retains the central theme of evolution across networks of connected genotypes. Rather than building to a dramatic unveiling of his theory of innovation, Wagner delivers his main argument after less than a third of the book; the remaining chapters each develop the theory around a specific concern, such as recombination or plasticity. This structure recalls Darwin's *Origin of Species*, in which the theory of natural selection was laid out by chapter four and then applied for the remaining 11 chapters. In retrospect, we can see the tremendous potential latent in those few simple ingredients that make up the idea of natural selection. But is Wagner's theory of the origins of innovation rich enough to warrant its own book? To answer this question, we have to appreciate the scope of Wagner's goals.

While Wagner sets out his explicit goals in an ambitious first chapter, the next three chapters give the first real glimpses of what this book is meant to accomplish. Wagner devotes 50 pages to a quantitative picture of the genotype networks that underlie metabolic systems, transciptionally regulated gene networks, and protein and RNA biomolecules. Drawing extensively on published work from the Wagner lab, these chapters establish the foundation of later arguments linking genotype networks to evolutionary innovation. This foundation is based on degeneracy – the property that many genotypes correspond to each phenotype – and the recognition that the genotypes in these networks may be functionally equivalent but mutationally distinct. This latter phenomenon, which reflects epistastic interactions among genes and sites within a gene, is a major theme in Wagner's earlier book as well, but here it forms the central pillar of a network-based theory of innovation.

One striking feature of these early chapters is the focus on quantitative results from numerical models. Numerous figures plot measurements like the relationships between genetic and phenotypic distances, or the distributions of the sizes of genotype networks. These simulations are based upon simplified models of fitness and mutational change and so it is difficult, at first, to appreciate the value of the exact quantitative details. These early chapters may be tedious for some readers, and indeed, Wagner advises that these chapters may be skipped. But while many of the numerical measurements he presents have only a loose relation to biology, the goal of his presentation is actually quite exciting: Wagner is trying to inculcate in the reader an intuition for the discrete, high-dimensional spaces that truly underlie evolution, and in the process trying to displace the dominant metaphor of adaptive landscapes.

The common metaphor of evolving populations seeking ''peaks'' on a landscape of fitness hills and valleys is both clearly problematic, and difficult to avoid. The concept relies on the mapping of possible genotypes onto two spatial dimensions, while fitness determines the height of each point. A population is then thought of as a point, or perhaps a small cluster of individuals, which moves up hills by natural selection and fluctuates down into shallow valleys by genetic drift. While making evolution seem easy to grasp, this metaphor also highlights an apparent problem: how can populations atop a modest hill move to an adjacent, higher peak, when any single change must require a drop in fitness?

The pathology of this metaphor for adaptive evolution has been recognized for a while. The atomic unit of genetic change is the substitution of a single nucleotide in one of the hundreds of base pairs that make up a typical gene. Each of these sites represents a possible direction of change, and a polygenic trait may contain not two but thousands of independent, orthogonal dimensions for the evolutionary process to search. This realization makes the existence of true ''peaks'' empirically unverifiable [9], but leaves open the possibility that complex adaptations require deleterious, ''downhill'' intermediate steps.

Wagner's main argument is that the generic properties of genotype networks – particularly their vast size and their interdigitation – obviate this problem entirely. Qualitatively different phenotypes may be separated by many steps, but most of these changes are only weakly selected. These neutral or nearly neutral paths bypass much of the apparent difficulty of the evolution of complex traits. While his calculations may seem abstract, their presence is the essential quantitative foundation for this new metaphor for adaptation.

While others have highlighted the significance of degeneracy for adaptation (e.g. [10]), the strength of Wagner's book lies in the clarity with which these ideas are elucidated, and especially in the great variety of empirical examples. Many exciting results of the last decade, from experimental evolution [11] and pathogen adaptation in nature [12, 13] in particular, take on broad significance in light of Wagner's arguments for the generality of genotype networks in evolution. Wagner devotes much of the book to illustrative examples from a very broad sampling of the evolutionary literature, and this willingness to engage with experiments will make his book much more accessible to molecular biologists than the average evolutionary monograph.

The breadth of his presentation, however, does at times lead to the impression that Wagner's theory may be a little too malleable. Wagner proposes observations about genotype networks that could have invalidated his theory, and he derives novel predictions, but these still do not add up to a readily falsifiable theory. Wagner's goal is actually more of a general explanatory framework, not a fully predictive theory, and so his presentation sometimes brushes past the potential importance of alternative factors that may germinate innovation. Factors such as gene duplication and horizontal gene transfer are discussed briefly, and filtered through the perspective of genotype networks. Wagner's eagerness to apply his overarching theory to much of evolutionary biology gives an enjoyable energy to the book, but readers should not expect that the theory of genotype networks will solve all of the questions of evolutionary innovation.

In fact, some readers may finish the book with a lingering doubt about whether Wagner has been discussing innovation at all. Sherlock Holmes once complained that his deductions seemed to change from mystical to trivial after each step had been explained, and similarly, a persistent problem to any such theory is that innovation loses it apparent novelty when we understand the incremental underlying process. The evolutionary steps on which Wagner focuses might be called microevolutionary. Consequently it seems reasonable to ask whether his theory has much bearing on some of the largest qualitative jumps in the history of life, such as the transition to multicellularity or the origin of consciousness. Though some readers may reject any general, incremental theory for the big innovations in their field, Wagner's perspective on genotype networks may eventually reveal the underlying logic to even the most dramatic novelties in biology. But for now, the link between the stepwise adaptation of Wagner's models and the major innovations of biology remains speculative.

This book will surely be influential with the next generation of evolutionary biologists, who will be able to digest and then apply the significance of a network-centric view of adaptation. Such a perspective will be essential for interpreting the increasing number of empirical studies that recapitulate evolutionary innovations in laboratory experiments. But even those molecular and evolutionary biologists who do not actively work on problems of innovation will benefit from the clarity of Wagner's theoretical arguments, and the inspiring wealth of empirical examples that demonstrate a new way to think of the dynamics of adaptation.

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