Biotech: The Countercultural Origins of an Industry

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Source: BioScience, 57(4) : 373-374

Published By: American Institute of Biological Sciences

URL: https://doi.org/10.1641/B570412

Themes on Variation

Variation: A Central Concept in Biology. Benedikt Hallgrímsson and Brian K. Hall, eds. Elsevier Academic Press, Burlington, MA, 2005. 592 pp. $74.95 (ISBN 9780120887774 cloth).

Darwin's engine, natural selection, requires fuel to drive it, and variation among individuals provides this fuel. Our mechanistic understanding of how the engine operates to transform populations has been enhanced by theoretical and empirical studies in population and quantitative genetics over many years. However, until recently, despite countless studies amassing data on the quantity and quality of the requisite fuel, no parallel body of theory and experiment on the origins and maintenance of variation has arisen. Over the past decade, authors in a variety of disciplines have begun to develop frameworks for understanding these issues. The editors of *Variation: A Central Concept in Biology,* Benedikt Hallgrímsson (University of Calgary, Alberta, Canada) and Brian K. Hall (Dalhousie University, Halifax, Nova Scotia, Canada), bring together a group of experts with a view toward building on these frameworks. Their own contributions emphasize the distinction between variability (the predisposition to vary) and variation, and focus on understanding the forces generating three patterns of variation: canalization, developmental stability, and morphological–developmental integration.

Peter Bowler opens with a fine overview of the history of ideas concerning variation. He begins with Darwin's views and contrasts them with those of Darwin's contemporaries. He then details the changes in viewpoint that evolved en route to the subsequent synthesis. The next chapter is an update by Leigh Van Valen of his 1978 classic "The Statistics of Variation." Following this section, chapters are loosely organized into three thematic areas: genetic and developmental determinants of variability, environmental determinants of variation, and comparative studies of variation.

Chapters by D. C. Jones and R. Z. German, Miriam Zelditch, and Ellen W. Larsen emphasize the importance of recognizing ontogenetic components of variation. Zelditch's chapter is noteworthy for her discussion of four biological hypotheses related to patterns of variation and canalization of skull shape: targeted growth, variation in developmental timing, modularity, and neural regulation. She provides a lucid presentation of the expected patterns and their causes, and the problems associated with distinguishing hypotheses that have overlapping predictions.

Canalization and constraint are covered in five chapters. Ian Dworkin contrasts what he refers to as two definitions of canalization, a reaction norm view and a variation view. He says that "at this point it is unclear which definition is in fact the correct one," but I would argue that both the across-environment and the within-environment perspectives are valid. Dworkin also raises the important issue of cryptic variation (what I call "hidden reaction norms") and discusses the issues of its genetic architecture and its role in evolution.

Hidden variation is again addressed by Ary A. Hoffman and John A. McKenzie when they review the concept of evolutionary capacitors, or mechanisms for storing variation for future release. I was a bit surprised in this chapter at the section heading "Do we need variability generators?"which seemed to me to be the wrong question to ask. Instead, we should ask, "What proportion of evolutionary change can be attributed to different sources of variation?" (i.e., new mutations versus hidden variation). Alexander Badyaev addresses this issue more directly by examining the issue of stress-induced variation (using examples in bumblebees and shrews) and how it may be integrated and accommodated by the organism.

The flip sides of canalization—plasticity and developmental instability (noise, asymmetry)—also receive explicit coverage in several contributions (e.g., A. Richard Palmer's tour of antisymmetry). Sonia Sultan and Steve Stearns's exposition on reaction norms is notable because it goes beyond the standard treatment of plasticity to address more explicit developmental themes, and it raises questions about how genetic variation for plasticity within different species can affect community-level processes such as competition and predation.

The concluding essays outline three distinct perspectives on future research agendas, and their similarities and differences are revealing. For example Hallgrímsson and Hall explicitly identify three patterns of phenotypic variation—canalization, developmental stability, and morphological integration. Phenotypic plasticity is never mentioned in the chapter; it appears to be implicitly included within canalization. David M. Parichy echoes that view, calling plasticity a "breakdown in canalization," but notes that it "has been profoundly understudied by mainstream developmental biology." In contrast, Samuel Sholtis and Kenneth Weiss explicitly include responses to the environment in their framework for the study of phenogenetics (i.e., how genotypes map to phenotypes). In this context, they suggest the importance of a phenomenon they term "phenogenetic drift": random changes in the genetic underpinnings of a specific phenotype. (This is akin to the idea of neutral networks discussed by Lauren Ancel Meyers earlier in the book; see also Ancel Meyers et al. 2005.) The result of this drift is that while phenotypes may change little or not at all, random genetic changes may be moving the organism toward other genetic boundaries where phenotypic change may be substantial. I agree that this is a key concept for our ultimate understanding of phenotypic evolution. Although Sholtis and Weiss's exposition of the many alternative routes between gene and phenotype may leave readers frustrated by the potential complexity, it is an accurate representation of the reality we need to accommodate.

One source of annoyance in this volume is the lack of a consistent terminology. Terms such as "canalization," "epistasis," and "developmental plasticity" are all used with multiple meanings. In some cases, individual authors take care to make their usages explicit, but in others it is clear that a different meaning is intended. A second peeve: I was nagged throughout this book by the glaring taxon bias. Zoologists (including anthropologists) wrote 20 of 22 chapters (including one that was coauthored with a botanist). This would pose no problems if there were no literature on variation in plants, fungi, and single-celled organisms (not so), or if the scholarship in the contributions extended to embrace the other literature. (In the most egregious example of exclusion, of 60 taxon-specified references in one conceptual chapter, 59 were to animals and only 1 to plants.)

As an overview and attempt at synthesis, I found the volume uneven. Reviews of developmental noise and antisymmetry get their own chapters, but mutation and recombination, topics that one might consider central to the study of variation and variability, are covered in five pages. Genetic and developmental sources of variability and variation get abundant coverage, but environmental sources seem marginalized. However, the majority of chapters are authoritative and well written, and graduate students and scientists will find much here that is thought-provoking.

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doi:10.1641/B570411
Include this information when citing this material.

FROM RESEARCH TO TECHNOLOGY

Biotech: The Countercultural Origins of an Industry. Eric J. Vettel. University of Pennsylvania Press, Philadelphia, 2006. 296 pp. $39.95 cloth (ISBN 9780812239478).

Biotech: The Countercultural Origins of an Industry appears in the University of Pennsylvania Press series on politics and culture in modern America. The series, edited by Glenda Gilmore, Michael Kazin, and Thomas Sugrue, proclaims that it is "motivated by a desire to reverse the fragmentation of modern U.S. history and to encourage synthetic perspectives on social movements and the state, on gender, race, and labor, on consumption, and on intellectual history and popular culture." Bravo to the editors for including the history of science and technology as central to US history.

The author of this volume, Eric J. Vettel, received his bachelor's degree in history from Stanford and his PhD from the University of Virginia, then returned to the Bay Area as a Bancroft Fellow in US history at the University of California, Berkeley. In 2005, he began serving as executive director for the Woodrow Wilson Presidential Library in Staunton, Virginia. Vettel's focus on history and his experiences in the Bay Area apparently shaped his decision to focus on the development of biotechnology research and industry in the San Francisco area.

Biotech offers a study of biological research in three Bay Area institutions, and of the move from the idealism of what was perceived as pure research to the development of the applied biotech industry. Berkeley, Stanford, and the University of California at San Francisco, the subjects of close analysis, exemplify the different types of universities responding to the expansion of research in the life sciences, with Cetus the example from the biotech industry. The implication is that because the biotech industry grew up in the San Francisco area, looking at the dominant institutions there will illuminate the origins of the industry.

The marketing claim on the book's dust jacket, that it "chronicles the story behind genetic engineering, recombinant DNA, cloning, and stem-cell research," is surely overplayed. Biotechnology also arose in other places, notably the Boston area, and to get a broader and richer historical understanding of the industry, we would surely need to look beyond the three universities and one industrial example discussed in *Biotech.* Furthermore, much genetic engineering, cloning, and stem cell research has migrated to the Bay Area only recently and certainly did not emerge there. Nonetheless, solidly grounded history starts with careful description of selected cases, and that is what Vettel gives us. From the aggregation, we can begin to build an understanding of the complex of factors that allowed the transformation of what the researchers thought of as pure university research into its application through the biotech industry.

Vettel starts in the 1940s, in the period following World War II and in the relatively sleepy research environment that emphasized the physical sciences much more than the life sciences. First Berkeley and then Stanford sought to hire strategically in biology to take advantage of emerging interests in genetics, DNA, proteins, and biochemistry. Berkeley bet on Wendell Stanley, with his self-centered emphasis on basic bench research on crystallized tobacco mosaic virus. President Sproul looked particularly inspired when Stanley received a Nobel Prize just as Berkeley was hiring him. Yet Vettel shows how that great hope soon turned to disappointment, as Stanley failed to understand how to cultivate patrons such as Warren Weaver at the Rockefeller Foundation. What could have become more than a million dollars in funding dwindled to a $150,000 equipment grant because of personal misplaying of the process. Soon, other research programs prevailed, Stanley's shining star faded, and Berkeley was left with a major investment in the wrong place. Meanwhile, Stanford invested in another individual researcher, Arthur Kornberg. Kornberg better understood how to build a team and how to cultivate other actors in the process, and Stanford expanded the leadership by hiring others such as Paul Berg, but the enterprise remained focused on the importance of pure basic research.

By looking at three institutions, Vettel can show us each institution against the background of national and state funding, yet also illustrate the similarities and differences among the central individuals, administrations, and communities with whom they interacted with varying degrees of success. It is the interplay among individuals, the struggle for existence and dominance of different labs and different research approaches, and the relative success of administrators in shaping the development the way they wanted that Vettel reveals so effectively.

The 1960s brought new struggles and increasing calls for publicly funded science to have social value. In 1968 Berkeley became a political battleground, with chaos and divisions across many lines in the university and between the university and its communities. Vettel demonstrates nicely that the demand for conscience in science brought a strong sense of concern for humanity to the sciences. And this, he notes, had surprising implications: "Ironically, it was these bioscience humanists, although occasionally unpopular for their imperialist tendencies in the 1960s, who would eventually become the handmaiden for a commercial bioscience industry in the coming decade" (p. 128).

Two chapters look at the shifts from pure research, first to an acceptance of the need for applied science, and later to demands for successful technological products. These chapters could have become muddled and overly complex—there is so much material, so many other historians have looked at pieces of this picture, and so many individual players have their own interests in constructing and reconstructing the stories—but the author does a nice job of keeping his story under control. Vettel needed to have a clear set of selection criteria in mind to maintain his focus, and he succeeded. This means that there is much more to be told, and we can look forward to other historians' contributions of additional and alternative perspectives.

Vettel's version is compelling, well documented, and important. He leads us to a short chapter on Cetus, which he labels "History's First Biotechnology Company." This chapter is necessarily a bit disappointing, if only because biotech companies are not inclined to let go of their secret negotiations and decisionmaking processes. We learn about the decisions, but less about the reasons for the choices made. The closing chapter offers a few pages on the story of the Asilomar Conference on recombinant DNA (a history that has appeared in much greater detail elsewhere, as Vettel knows) and a few pages of reflections. Instead of offering conclusions about what his case analysis means, however, Vettel ends by acknowledging that biotech development has its attractions and promises for improving our lives, while it also carries risks and costs.

This acknowledgment is hardly profound, but I think it constitutes one of the best features of this well-written book: Vettel does not succumb to reaching for bold and overdrawn conclusions, he does not moralize, and he does not preach. In giving us solid, empirically driven descriptive history and detailing episodes in the history of life sciences that have helped shape the way biotech has emerged, he gives readers something more substantial and more likely to retain its significance than overblown conclusions. He does not pretend that he has the answers; as he notes, we are only beginning to understand the questions. That is what makes this book appealing: It helps us begin to see some of the complex questions that we will have to address in deciding how much and which basic research, applied science, and technological application we want.

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doi:10.1641/B570412
Include this information when citing this material.

THE EVOLUTION OF EVOLUTIONARY GENETICS

Evolutionary Genetics: Concepts and Case Studies. Charles W. Fox and Jason B. Wolf, eds. Oxford University Press, New York, 2006. 608 pp., illus. $59.50 (ISBN 9780195168181 paper).

We evolutionary geneticists hold the history of our field nearly sacred. For example, one of my mentors referred to Ronald Fisher, Sewall Wright, and J. B. S. Haldane as the "holy trinity" of evolutionary genetic theory. Theory that emerged from the modern synthesis and later in the molecular revolution spearheaded by Motoo Kimura has served us well for nearly a century, and is arguably unsurpassed in biology in its elegance and explanatory power. The last two decades have ushered in rapid technological changes in the field concurrent with the development of the polymerase chain reaction and rapid genomic sequencing. These advances have given us unprecedented comparative data and insight into the workings of evolution at the nucleotide, gene, gene-network, and whole-genome levels.

Some new insights have suggested that this substantial body of evolutionary theory may still be useful but sometimes inadequate, or at worst, misleading to our understanding of how genes, genomes, and phenotypes are integrated and evolve. The question for the field is, How tightly should we cling to our past? Is modern synthesis–era theory still useful, and if so, when? What kinds of adjustments or modifications to evolutionary genetic theory have been or need to be made, and what are the empirical observations that motivate such changes? *Evolutionary Genetics: Concepts and Case Studies* endeavors to address these issues directly.

Editors Charles W. Fox (University of Kentucky) and Jason B. Wolf (University of Manchester) have assembled an impressive compendium of essays that can be loosely categorized into two main themes: (1) evaluation of principles, pitfalls, and developments in analytical methods of inquiry, and (2) new problems and conceptual directions in evolutionary genetics. Entries in the latter category are usually (but not always; see chapter 23, by Steven A. Frank) motivated by comparative genome-level analysis. This book is intended to be a companion volume to *Evolutionary Ecology: Concepts and Case Studies* (2001), also coedited by Fox. While there is some overlap in the topics treated by these two books (and a recurrence of some authors in this volume), the approaches to questions and empirical examples are strikingly different.

Fox and Wolf study invertebrates, so it is not surprising that this book relies heavily on results obtained from a classic model system in evolutionary biology: the fruit fly, *Drosophila.* I first thought that this relatively narrow focus was a weakness. It occurred to me, however, that many of the chapter authors who use *Drosophila* in their work also happen to be among the most prolific and thoughtful researchers in evolutionary genetics. It is thus natural for the book to focus predominately on this model system, as most of our understanding about how genomes integrate and translate into phenotypes has emerged from study of such systems. The challenge for researchers who examine nonmodel systems (as I do) will be to evaluate how and when we can apply knowledge obtained from models to our own research (e.g., chapter 15, by David L. Stern). This is an area of intensive investigation and will undoubtedly be the subject of books in the near future. I learned a lot from *Evolutionary Genetics: Concepts and Case Studies,* and I encourage evolutionary biologists of all stripes to read it.

The book is arranged in 32 chapters and six parts, beginning with the basics of evolutionary theory, empirical observations, and the rationale for fundamental tenets of the field. The first section, "Principles of Evolutionary Genetics," provides an introduction to the kinds of forces (i.e., mutation, genetic drift, and natural selection) that operate to change genotypic and phenotypic frequencies in populations. Chapters 2, 3, and 4 effectively and concisely lay the groundwork for the chapters that follow in other sections.

It is in these chapters, however, that I found the information boxes (included in nearly all of the book's 32 chapters) to be distracting. Boxes are ostensibly included either to treat topics that are outside the area of expertise of the chapter authors or to provide concise descriptions of topics that could not otherwise be covered in the chapter because of length restrictions. However, the boxes sometimes spanned several pages and digressed to an extent that detracted from the flow of some chapters. This is not to say that the boxes were poorly written or uninformative, but that they were best integrated and most readable when they were short (one page or less) and tightly reined by the goals of the chapter. John H. Gillespie's chapter (chapter 5) is a good example of effective use of boxes. (As an aside, I also found Gillespie's chapter to be inspiring and provocative, especially to those of us who wish to use coalescent theory to estimate demographic parameters from genetic variation in natural populations.) Information boxes notwithstanding, the editors do a commendable job of providing uniformity and continuity of chapter organization, which makes this compendium highly readable in general.

A major emphasis of the book is examining the use of quantitative genetic approaches for the integration of genotype and phenotype, and this topic is evaluated to some degree in all six sections. At least 11 of 32 chapters develop analytical and empirical approaches to study two crucial but comparatively poorly understood features of gene interactions: pleiotropy and epistasis. It is difficult to overstate the importance of these gene-by-gene interactions. A full understanding will help us to detail the workings of gene networks more fully (e.g., chapter 13, by Simon C. Lovell) and to understand robustness to mutation and developmental canalization (e.g., chapter 16, by Mark L. Siegal and Aviv Bergman). Accordingly, rich analytical and empirical toolboxes to document the outcomes of epistatic and pleiotropic interactions are a linchpin for advancing the field of evolutionary genomics and proteomics.

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Two sections of the book, "Genetics of Speciation" and "Evolutionary Genetics in Action," captured my attention and imagination. Most attractive was the sheer variety of topics treated in these sections, ranging from the coevolution of hosts and parasites (chapter 29, by Paula X. Kover) to the role of hybridization as a creative force in evolution (chapter 26, by Michael L. Arnold and John M. Burke). The chapter by Daniel E. L. Promislow and Anne M. Bronikowski (chapter 30, "The Evolutionary Genetics of Senescence") was an intriguing combination of life history theory and genetics for examining hypotheses regarding the evolution of senescence. Finally, the chapter on experimental evolution (chapter 31), by Adam K. Chippindale, provided a concise vision of the power of model systems to examine genotypic and phenotypic change over evolutionary timescales (i.e., over many thousands of generations). In all, I was impressed with the holistic and synthetic nature of the chapters in these sections and felt they were a perfect way to draw together the preceding sections into a wonderful finish.

This book does what it sets out to do. It clearly lays out where the field of evolutionary genetics has been, develops theoretical and analytical modifications of modern synthesis–era theory that fully encapsulates new empirical knowledge, and provides an enticing glimpse of the future direction of the field.

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doi:10.1641/B570413
Include this information when citing this material.

NEW TITLES

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