

BOOK REVIEW**A path to success? A review of *evolution, development, and the predictable genome* by David L. Stern****Hope Hollocher,^{a,*} Charles H. Pence,^b Grant Ramsey,^c and Michelle M. Wirth^d**^a Department of Biological Sciences, Galvin Life Sciences, University of Notre Dame, Notre Dame, IN 46556, USA^b Program in History and Philosophy of Science, John J. Reilly Center for Science, Technology and Values, University of Notre Dame, Geddes Hall, Notre Dame, IN 46556, USA^c Department of Philosophy, University of Notre Dame, Malloy Hall, Notre Dame, IN 46556, USA^d Department of Psychology, University of Notre Dame, Haggard Hall, Notre Dame, IN 46556, USA

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Evolution, Development, and the Predictable Genome: Stern, David L. 2011. Roberts and Company Publishers, Greenwood Village, CO. xvi + 264 pp. \$40.50; ill.; index. ISBN: 978-1-936221-01-1.

David Stern's book, *Evolution, Development, and the Predictable Genome*, is a bold attempt to synthesize population genetics and developmental biology. The synthesis that Stern hopes to accomplish is as difficult as it is necessary. The two disciplines have famously divergent histories, approaches to problems, and views on what constitutes important biological questions. Further, many such "new syntheses" have worked only at integrating evolution with development—for example, considering its role in the production of evolutionary adaptations—on a macroevolutionary scale. The tools of population genetics have not, in general, been party to these efforts.

The perspective developed in this work is intended to have several novel features. First, it aims to be substantially more mechanistic than similar works, focusing on single lineages of gene regulation (termed "pathworks") extracted from the broader developmental networks directly responsible for the production of a given morphological trait. Second, it brings more micro-evolutionary focus to developmental biology, spending substantial time discussing the consequences of population-level phenomena on the evolutionary genetic bases of morphological traits. Finally, it follows a recent pedagogical trend (see also, e.g., Bateson and Gluckman 2011) in being what we might call "concept-focused." Each of its beginning chapters focuses on fundamental concepts in population genetics and developmental biology; the book then ends with synthetic chapters that weave these otherwise disconnected concepts together into a more

comprehensive, global view of the evolution of developmental traits.

As should be apparent from this brief overview of Stern's project, the task that Stern has set for himself is highly ambitious. To present such a synthesis at all—much less to make it accessible in book form—is a serious challenge. Stern notes in his introduction that he produced several complete drafts of the work before settling on the structure of the published version. The end result is a highly readable narrative that is a cross between a more conventional textbook and a complex treatise, reflecting strongly Stern's intellectual development as a researcher whose own work straddles these two rather disparate worlds. Stern uses simple language to introduce population genetics in a way that is free of equations in order not to scare off those not familiar with the mathematics behind population genetics. The population genetics concepts that are emphasized, such as dominance, pleiotropy and epistasis, are not ones typically considered in other synthetic approaches, and they are explained clearly, providing helpful overviews for molecular and evolutionary biologists alike. Stern also introduces molecular and developmental concepts using similarly accessible language, moving from what DNA is to how regulatory networks work in developing organisms with the same easy clarity.

Although the readability of the book is beneficial, it also has its downside. Stern is subtle in making his points, and it is easy to miss the profound implications of some of the more nuanced arguments. This is especially true for the uninitiated reader, and for members of the book's professed audience: senior undergraduate and beginning graduate students with no formal training in evolutionary or developmental biology. Simple language may lead the reader to think that the concepts are

equally simple, though this is often not the case. Further, it would have been a great help if the first chapter introduced a clearer picture of the payoff of the pathworks framework (addressing such questions as, “Why would it make evolution predictable?” and “Why is it superior to alternative approaches?”). The book lacks this overall guide to the structure of the ensuing chapters, as well as smaller signposts throughout to remind the reader of their final destination. Each chapter possesses a summary, but the summaries do not make plain the contribution of each to the major synthesis of the book. In that respect, readers can come away with less than is actually being offered and can feel underwhelmed by the final conclusion.

Stern’s unique contribution to the synthesis of evolutionary and developmental biology lies in his proposed pathworks analysis. This approach promises to predict where in the developmental network mutations will preferentially accumulate during morphological evolution. Instead of treating alleles as generic entities whose dynamics follow from the equations of population dynamics, Stern argues that there are “hot spots” for the mutations underlying evolution, and that these hot spots are predictable given the topology of the gene networks. Because an individual gene network is too complex to study as a whole, Stern proposes a more experimentally tractable approach: to trace the single lineage of gene regulation necessary to develop a specific cell type. For example, we might trace a single gene regulation pathwork necessary for the formation of a bristle in a single cell, as opposed to considering the entire regulatory gene network associated with bristle formation more generally. Via the pathworks framework, one is able to identify the key genes that integrate regulatory information and will be more likely to have pleiotropic consequences developmentally, greatly influencing the course that natural selection will likely take. The goal would be to use the pathworks framework to predict which regulatory genes would be more likely to accumulate mutations generating morphological change, and then to place these data into a population genetics framework to be able to make long-term evolutionary predictions. Stern also strongly argues that pathworks alone cannot predict evolutionary outcomes for developmental traits, pointing out that population processes also play a critical role in either strengthening or relaxing the constraints posed by different classes of mutations with respect to their dominance, pleiotropic and epistatic effects. Stern rightly emphasizes that it is only with this dual perspective that one can fully understand the dynamics of molecular change underlying morphological traits.

The benefits of taking this approach are obvious. Arguably, any method by which we can reduce the level of complexity normally found in studies of regulatory networks (such as the famous sea-urchin work by Davidson et al. 2002) is much appreciated, and Stern’s pathworks analysis certainly succeeds at making that complexity manageable. The notion borrows both from lineage analysis in evolutionary studies and network analysis in developmental genetics. However, its reliance on

total knowledge of molecular, developmental, and population genetic processes is too demanding to make it a useful tool for predicting genome evolution more generally. Although Stern’s are laudable goals, our knowledge base is still too underdeveloped to be able to take full advantage of this approach outside of the handful of studies illustrated in the book, each of which represents years of painstaking research. Not all researchers will be able or wish to adopt such a strategy, and it is not necessarily advisable that they do. Greater advances can probably be made in the field by employing a variety of approaches. For example, strides have been made at the opposite extreme through the development of quantitative and genomic algorithms that directly incorporate global epistasis in the analysis of regulatory networks underlying complex traits (e.g., Hu et al. 2011).

Given these limitations, the “predictability” in Stern’s title applies to very few systems. Some predictions about the genome can be made using gene regulation pathworks, though these will need to be tested more rigorously. As presented, the pathworks approach seems to have the most explanatory power in retrospect (e.g., the contrast between bristle evolution in *Drosophila* larvae and the evolution of vernalization in *Arabidopsis*). Even the canonical example of using pathworks to predict bristle evolution in *Drosophila* larvae is complicated by the fact that the member species of this group are characterized by vastly different demographic histories which have not been taken into account in the analyses. Other factors that many researchers think are central to studies of evolution and development, such as plasticity and epigenetics, are also essentially ignored, adding complexity to the story that is not being considered. All these issues conspire to make Stern’s approach very genetically deterministic, despite the fact that development is more malleable than such an approach implies. In the end, the context-dependence of evolutionary processes is inescapable. Nowhere is this point driven home more strongly than at the end of the final chapter when, after having argued for predictability throughout the book, Stern notes that “perhaps—just perhaps—while most populations evolve obediently through fixation of mutations with specific effects, small populations, while teetering toward extinction and irrelevance, provide cauldrons of evolutionary novelty” (p. 173). In the absence of a better method either to decide which contributing factors will dominate the evolutionary process or to determine how these factors will interact more specifically, Stern seems to want to have it both ways—with predictability and chance both playing major roles in evolutionary change.

One of Stern’s most profound insights comes from the meta-analysis he provides in the final chapter of the book on the types of mutations that accumulate on different time scales. Traditionally, we use data from studies of within-species heterogeneity to learn about the basis for differences among species—extrapolating on the assumption that these two types of variation are essentially similar. However, Stern shows us here that while most of the mutations underlying *long-term* evolution

are regulatory, the vast majority of mutations underlying *short-term* evolution are *not* regulatory (see also Stern and Orgogozo 2008, 2009). Therefore, short-term, within-species variation is quite different from the long-term changes that move to fixation in entire species. Further, and unexpectedly, it is the *within*-species variation that runs *more* contrary to the constraints normally posed by pleiotropy, dominance, or epistasis, while long-term variation responsible for species differences is more well-behaved. If this generalization proves to be true, then this insight could fundamentally change how we approach the evolution of morphology and our concepts of the genetics underlying speciation more globally.

Stern's book provides food for thought on many levels for those who read the text carefully. And while the promise of making morphological evolution highly predictable might not be realized, this may not have been Stern's goal after all—but rather our unrealistic expectation as readers. Whether or not one supports Stern's pathworks analysis, there is great value in this approach as a first step towards achieving the Herculean goal of synthesizing evolution and development on a more mechanistic

level that can successfully take population genetics into account. A synthesis of these two fields along the lines Stern proposes has been too long in coming. Stern is asking all of the right questions, and the book outlines one possible path toward the answers we so desperately seek.

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