THE ULTIMATE CAUSES OF PHENOTYPIC INTEGRATION: LOST IN TRANSLATION[1]

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Hence if a man goes on selecting, and thus augmenting, any peculiarity, he will almost certainly modify unintentionally other parts of the structure, owing to the mysterious laws of correlation. (Darwin 1859)

Since Darwin's time we have come to recognize two major proximate causes of genetic correlation within populations (pleiotropy and linkage disequilibrium). Today's challenge, taken up by *Phenotypic Integration,* is to understand the ultimate causes of phenotypic and genetic correlation. A major advance on this front was made by Olson and Miller (1958) who proposed that phenotypic correlations between morphological structures may often reflect functional interactions. Olson and Miller's insight reverberates today as the first clear proposal for an ultimate cause of correlation. Olson and Miller coined the term *morphological integration* to describe character correlations that are shaped by selection. The first genetic model of morphological integration was constructed by Lande (1980). Lande was unable to derive a general expression for how genetic correlations evolve from generation to generation. Nevertheless, he was able to characterize the additive genetic variance-covariance matrix (**G**-matrix) at equilibrium as it pulsates and wobbles under the opposing forces of mutation, recombination, and selection. Among other things, the resulting expression identifies correlational selection (selection that directly changes the covariance between two traits) as the major selective force shaping the evolution of genetic correlation and hence morphological integration. In an important early implementation of Lande's (1980) results, Cheverud (1982) showed how morphological integration could be pursued in a quantitative genetic framework. For many years, Cheverud and his colleagues seemed to be the only modern champions of morphological integration. Thus, Pigliucci and Preston's book, *Phenotypic Integration,* brings welcome attention to empirical laws of correlation that remain, in many ways, mysterious.

Phenotypic Integration brings together contributions from empiricists and theoreticians, botanists and zoologists, and carries a strong multivariate theme throughout its 19 chapters. The term *phenotypic integration* is a welcome broadening of morphological integration to include behavior and other kinds of nonmorphological traits. Does this volume introduce a new theory of phenotypic integration? Not only is the answer ''No!'', in several chapters this volume steps backward more than two decades, as the authors create new conceptual muddles and needlessly fret over issues that have long enjoyed

analytical solution. Nevertheless, despite these and other disappointments, the volume has its strong points.

This volume includes several outstanding chapters. The second to last chapter, by K. Schwenk and G. P. Wagner, deserves to be read first. The authors point out that attempts to explain evolution in terms of selection or constraint are based on a false dichotomy. The dichotomy fails because many constraints may themselves be products of selection or, as Schwenk and Wagner put it, ''Constraints are forged in the fires of selection.'' T. F. Hansen and D. Houle contribute a thought-provoking chapter on the problem of stasis. While acknowledging that stabilizing selection is the leading candidate explanation for stasis, Hansen and Houle cogently argue that we still need to know a lot more about stabilizing selection. In particular, we need to understand why the position of the adaptive peak varies only within a narrow range, sometimes over vast stretches of geological time. In another chapter, J. Merilä and M. Björklund provide the best summary in the book of relevant theory and also show how this theory can be applied in test cases. Finally, J. B. Wolf, C. E. Allen, and W. A. Frankino give a lucid explication of Sean Rice's phenotypic landscape (not to be confused with the adaptive landscape, discussed below) and illustrate how the concept can be applied to a wide range of topics and issues.

Many other chapters in the book are worth reading and together they cover a broad territory that includes discussions of modularity, allometry, plasticity, multivariate results from QTL studies, mutation, heterochrony, theory, and philosophy. The reader should not expect, however, a tightly integrated volume. The editors have provided brief introductions to the five parts of the volume but very little in the way of overview and synthesis. The bigger problem is that the authors are unaware of each others' perspectives and contributions. One encounters outright contradictions from chapter to chapter. Furthermore, the variance in chapter quality is huge. We are clearly in the early days of our understanding of phenotypic integration, so it may be useful to catalog the volume's conspicuous failures.

The most fundamental problem with *Phenotypic Integration* is its general failure to incorporate—or even portray—relevant historical and contemporary developments in theory. Nothing is harder to grasp than someone else's theory, and we are all guilty of overlooking important conceptual papers. Nevertheless, the oversights in this volume are so egregious that the big picture in evolutionary quantitative genetics has been almost completely lost. From this standpoint the most glaring omission in the book is the adaptive landscape and the role that it plays in shaping phenotypic integration. The history of the Simpson-Lande adaptive landscape for phenotypic traits and its importance as an integrative concept have been recounted elsewhere (Arnold 1992, 2003; Arnold

et al. 2001). Most importantly, analytical and simulation work has shown that curvature and movement of the adaptive peak can drive the evolution of inheritance and mutation matrices, as well as the phenotypic mean (Lande 1976, 1979, 1980, 1984; Bürger and Lande 1994; Jones et al. 2003, 2004, et seriatim). It's not as if the adaptive landscape were just one in a field of contenders for the ultimate explanation of phenotypic integration: one could argue that it's the only contender! Equally puzzling is the absence of direct empirical tests of Olson and Miller's (1958) central proposition that morphological integration reflects functional connections and hence the history of selection acting on a suite of characters. Such tests would compare the pattern of multivariate stabilizing selection (embodied in the γ-matrix) with the pattern of phenotypic or genetic covariance (e.g., Brodie 1992). Such tests are alluded to in a few places in this volume, but no one delivers the goods. Other missed opportunities pale in comparison to these, but are nevertheless wrenching.

Among the painful omissions is the function-valued approach to phenotypic plasticity and ontogeny. In this approach, also known as the infinite-dimensional approach, phenotypic traits that vary as a function of age or environment are represented by continuous functions. The approach departs from earlier attempts to force the phenotype into preformed molds (e.g., von Bertalanffy growth functions) by letting the data themselves define the functions and by letting **P**- and **G**-matrices, as well as selection, take continuous forms (Kirkpatrick and Heckman 1989; Kirkpatrick and Lofsvold 1989; Gomulkiewicz and Kirkpatrick 1992; Kingsolver et al. 2001). A big push (funded by the U.S. National Science Foundation) is underway to enlarge the domain of the function-valued approach and to make its implementation easier. The absence of this perspective in this volume gives the treatments of plasticity and allometry an outdated feel.

Beneath the calm surface of quantitative genetics, controversy roils over the most appropriate model to account for the heritable variation that lies in abundance beneath most phenotypic traits. In fact, the surface is so calm that the controversy over the maintenance of genetic variation and covariation is barely acknowledged, much less explored in *Phenotypic Integration.* The standard approach to this problem has been to assume that stabilizing selection acts on one or more traits and ask what distribution of mutational effects (e.g., Gaussian or non-Gaussian) could account for the observed genetic variance at equilibrium (Bürger 2000). Recent tests of the adequacy of this kind of mutation-selection balance have used models in which inheritance is more than simply additive. Hermisson et al. (2003) make the important point that the evolution of pleiotropic effects requires epistasis, and they develop a model to explore the consequences of this idea. They find that epistasis reduces the magnitude of genetic variance at equilibrium, but increases the magnitude of mutational variance. Zhang et al. (2004) argue that a model with dominance adds support to the proposition that genetic variance is maintained by mutation-selection balance. Although the controversy over the maintenance of genetic variation and covariation has seemed irreconcilable, studies of mutation accumulation, QTL distribution, and directed mutagenesis of proteins are edging us closer to a resolution. It's time to tune in on current work on this issue. How does

this underlying controversy bear on the field of phenotypic integration? It is absolutely fundamental. At issue is the development of a model that can account for phenotypic integration!

Recent simulation work on **G**-matrix evolution and stability is alluded to in one or two places, but the messages from those studies are not delivered. These simulation studies allow an escape from some long-standing limitations of analytical work. In particular, simulations allow us to determine whether—and how rapidly—the **G**-matrix evolves in response to change in the configuration of the adaptive landscape. Simulations confirm Lande's (1980) theoretical predictions that the equilibrium **G**-matrix is a compromise between the multivariate input from mutation and erosion and shaping due to stabilizing and correlational selection (Jones et al. 2004). Simulations also can help define the conditions under which the **G**-matrix is likely to be evolutionarily stable or prone to wildly erratic behavior. The simulations that have been conducted so far have shown that different aspects of stability respond differently to various determining factors (Jones et al. 2003, 2004). Thus, large population size promotes stability in the size of the **G**-matrix (i.e., stability in the sum of its eigenvalues), whereas a stable pattern of strong correlational selection promotes stability in the shape of the **G**-matrix (i.e., stability of its eigenvectors). Thus, simulation work raises a new series of empirical issues concerning the prevalence of factors that induce evolutionary change in the **G**-matrix or promote its long-term stability.

What, then, is the agenda for empirical work in the field of phenotypic integration? The Pigliucci and Preston volume offers some direction here but relatively little in the way of a program for dealing with the ultimate cause, selection. If we focus on selection as it is embodied in the adaptive landscape, several outstanding empirical issues rise up before us. (1) Is the adaptive landscape prone to long-term stability? Although it is clear that long-term stability in the position and multivariate curvature of the adaptive peak can promote long-term stability in phenotypic integration (Jones et al. 2003, 2004), the actual stability of the adaptive landscape is an open, empirical issue. Comparative studies of adaptive landscapes on a variety of timescales are desperately needed to address this stability issue. (2) Does landscape stability account for observed instances of **G**-matrix stability? **G**-matrix comparisons often reveal common principal components (stable eigenvectors) (Arnold and Phillips 1999). Is this kind of stability a consequence of stability in the curvature and orientation of the adaptive landscape, as simulation studies would suggest? (3) Does the mutation matrix evolve in relation to the adaptive landscape? Multivariate stabilizing selection on a suite of characters should exert indirect selection on the mutational process that produces pleiotropic effects (Wagner 1996; Wagner and Altenberg 1996). Is there enough heritable variation in pleiotropic mutation for this indirect selection to mold the evolution of the mutation matrix in predictable ways? (4) Do phenotypic reaction norms and allometric curves coincide with ridges in the adaptive landscape? The adaptive landscape perspective provides an obvious explanation for reaction norms and allometric curves. These phenotypic and genetic functions should coincide with ridges or tubes in the adaptive landscape. A current challenge

is to measure multivariate selection on reaction norms and allometries to see if this proposition holds.

Phenotypic Integration provides an arresting overall lesson for students and researchers who are trying to find their way in this field: don't rely on texts and contributed volumes to portray the current state of theory. As this volume vividly illustrates, there is no substitute for conceptual literacy and a command of the current theoretical literature. In particular, it's worth taking the trouble to learn a few basics of matrix algebra, so that you can read the primary theoretical literature. Bypassing this literature will inevitably mean that a lot will be lost in translation.

Literature Cited

Arnold, S. J. 1992. Constraints on phenotypic evolution. Am. Nat. 140:S85–S107.

———. 2003. Performance surfaces and adaptive landscapes. Integr. Comp. Biol. 43:367–375.

Arnold, S. J., M. E. Pfrender, and A. G. Jones. 2001. The adaptive landscape as a conceptual bridge between micro- and macro-evolution. Genetica 112/113:9–32.

Arnold, S. J., and P. C. Phillips. 1999. Hierarchical comparison of genetic variance-covariance matrices. II. Coastal-inland divergence in the garter snake, *Thamnophis elegans*. Evolution 53:1516–1527.

Brodie, E. D., III. 1992. Correlational selection for color pattern and antipredator behavior in the garter snake *Thamnophis ordinoides*. Evolution 46:1284–1298.

Bürger, R. 2000. The mathematical theory of selection, recombination, and mutation. John Wiley & Sons, New York.

Bürger, R., and R. Lande. 1994. On the distribution of the mean and variance of a quantitative trait under mutation-selection-drift balance. Genetics 138:901–912.

Cheverud, J. M. 1982. Phenotypic, genetic and environmental morphological integration in the cranium. Evolution 36:499–516.

Darwin, C. 1859. The origin of species. John Murray, London.

Gomulkiewicz, R., and M. Kirkpatrick. 1992. Quantitative genetics and the evolution of reaction norms. Evolution 46:390–411.

Hermisson, J., T. F. Hansen, and G. P. Wagner. 2003. Epistasis in polygenic traits and the evolution of genetic architecture under stabilizing selection. Am. Nat. 161:708–734.

Jones, A. G., S. J. Arnold, and R. Bürger. 2003. Stability of the **G**-matrix in a population experiencing stabilizing selection, pleiotropic mutation, and genetic drift. Evolution 57:1747–1760.

———. 2004. Evolution and stability of the **G**-matrix on a landscape with a moving optimum. Evolution 58:1639–1654.

Kingsolver, J. G., R. S. Gomulkiewicz, and P. A. Carter. 2001. Variation, selection, and evolution of function-valued traits. Genetica 112–113:87–104.

Kirkpatrick, M., and N. Heckman. 1989. A quantitative genetic model for growth, shape, reaction norms, and other infinite-dimensional characters. J. Math. Biol. 27:429–50.

Kirkpatrick, M., and D. Lofsvold. 1989. The evolution of growth trajectories and other complex quantitative characters. Genome 31:778–783.

Lande, R. 1976. The maintenance of genetic variability by mutation in a polygenic character with linked loci. Genet. Res. Camb. 26:221–235.

———. 1979. Quantitative genetic analysis of multivariate evolution, applied to brain-body size allometry. Evolution 33:402–416.

———. 1980. The genetic covariance between characters maintained by pleiotropic mutation. Genetics 94:203–215.

———. 1984. The genetic correlation between characters maintained by selection, linkage and inbreeding. Genet. Res. Camb. 44:309–320.

Olson, E. C., and R. L. Miller. 1958. Morphological integration. Univ. of Chicago Press, Chicago, IL.

Wagner, G. P. 1996. Homologues, natural kinds and the evolution of modularity. Am. Zool. 36:36–43.

Wagner, G. P., and L. Altenberg. 1996. Complex adaptations and the evolution of evolvability. Evolution 50:967–976.

Zhang, X.-S., J. Wang, and W. G. Hill. 2004. Influence of dominance, leptokurtosis and pleiotropy of deleterious mutations on quantitative genetic variation at mutation-selection balance. Genetics 166:597–610.

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