Evol Biol (2008) 35:182–185
DOI 10.1007/s11692-008-9027-6

COMMENTARY

Macroevolutionary Quantitative Genetics? A comment on Polly (2008)

Thomas F. Hansen

Received: 27 May 2008 / Accepted: 29 May 2008 / Published online: 19 August 2008

Arnold et al. (2001) saw the adaptive landscape, the relation between phenotype and fitness, as the bridge from microevolution to macroevolution. While it is not difficult to agree that a dynamical theory of the adaptive landscape is a necessary part of an operational theory of macroevolution, we also need another bridge from genotype to phenotype to operationalize the role of constraint in our macroevolutionary theory. David Polly (2008) is to be congratulated for his constructive comments on how such a bridge can be constructed by augmenting evolutionary quantitative genetics with morphometric and developmental models of the genotype-phenotype map.

Of course, this is not a new idea; evolutionary biologists have long tried to incorporate more explicit representations of the genotype-phenotype map (e.g. Lewontin 1974; Riska 1986, 1989; Slatkin 1987; Wagner 1989; Houle 1991, 2001); but these models have not become as central as they should, and the new understanding of development and gene regulation embodied in evolutionary developmental biology holds the promise of developing much better models both for general genetic and physiological networks, and for specific organ systems. Polly argues that such models may lead to evolutionary dynamics that are qualitatively different from that generated by the simple statistical genotype-phenotype maps of classical quantitative genetics. In this he is undoubtedly right. Here, I provide some further comments on how models of the genotype-phenotype map can enrich evolutionary quantitative genetics, but I also warn against the temptation to think that highly specific developmental models can replace the abstract quantitative genetics style of thinking.

Evolutionary quantitative genetics arose from the theoretical models of Russ Lande (e.g. Lande 1979). Lande argued that the pattern of additive genetic variances and covariances, the G-matrix, may be rather stable, and developed models of evolutionary dynamics based on this assumption. Importantly, these models also operationalized the study of selection in natural populations through the concept of a selection gradient (Lande and Arnold 1983).

These models are based on an additive, polygenic genotype-phenotype map. The "effect" of an allele is the average deviance from the population mean of individuals carrying that allele, and these effects are assumed to combine additively. The consequences of additivity for evolutionary dynamics cannot be overemphasized. It means that the phenotypic effect of an allelic substitution will be the same regardless of the genetic background in which it takes place, and thus regardless of where the population finds itself in phenotype space. In a polygenic model with a large or infinite number of possible allelic substitutions, this leads to open-ended, continuous evolution where any phenotypic change, no matter how large, can be generated in a relatively short amount of time.

Sometimes biologists without statistical training will dismiss the additive model with the argument that genes exert their effects through highly nonlinear physiological interactions. It is almost guaranteed, however, that the additive model will be a good local approximation to the genotype-phenotype map for segregating genotypes. This is due to the statistical definition of gene effects as averages over the genotypic combinations in which they occur. Even if the effect of a particular gene substitution may be different in different specific genetic backgrounds, the averaging over all backgrounds minimizes the variation

T. F. Hansen (✉)
Department of Biology, Centre For Ecological and Evolutionary Synthesis, University of Oslo, P.O. Box 1066, Blindern, 0316 Oslo, Norway
e-mail: Thomas.Hansen@bio.uio.no

due to gene interactions. Furthermore, dynamical models of the selection response show us that these average effects are precisely what we need to determine the changes in allele frequency (e.g. Bürger 2000). Consequently, we should not be surprised that the additive model shows good empirical fit (Hill et al. 2008), and that it is a good predictor of the short-term evolutionary response to selection on a trait by trait basis, although it should be admitted that its performance on predicting correlated responses is more mixed (Roff 2007).

The relevance of the G-matrix, hence, does not hinge on a strictly additive genotype-phenotype map. The G-matrix describes the variation in the average effects of segregating alleles, and thus the variation that selection can usefully act upon. Even with a highly nonlinear genotype-phenotype map, the G-matrix will be the best first approximation to the direction of evolution.

Where the complexity and nonlinearity of the genotype-phenotype map become essential is when we are looking at large changes in the phenotype, as for example when we aim to predict the course of macroevolutionary change. If we imagine a population undergoing a large evolutionary change, the G-matrix may remain a good predictor of evolvability at any point in its trajectory, but systematic nonlinearities in the genotype-phenotype map will systematically change the average effects of alleles, which again will systematically change the G-matrix. I here leave aside the complication that the G-matrix may also fluctuate transiently due to changes in frequencies of segregating alleles.

Thus, to extend evolutionary quantitative genetics from a theory of standing variation and short-range microevolution to a theory of macroevolutionary change, we need explicit representations of the genotype-phenotype map.

I find it useful to distinguish three different types of representations of the genotype-phenotype map. The first is the statistical representation. This includes models where gene effects are defined statistically based on segregating variation. The classical quantitative genetics model with gene effects as population averages or regression coefficients, and types of interactions measured as variance components, is of this type (see e.g. Lynch and Walsh 1998). The second representation we may call 'functional'. The conceptual distinction between statistical and functional representations was pioneered by Cheverud and Routman's (1995) model of 'physiological epistasis'. The idea here is that the effect of genotypic changes should be defined independently of what genes are segregating in the population. Note that this is in effect what is done in classical population genetics models, where specific phenotypes are postulated for each possible genotype in the model. Hansen and Wagner (2001) showed that this requires defining effects relative to a designated reference genotype, and developed a more general representation of this type (see also Barton and Turelli 2004; Alvarez-Castro and Carlborg 2007). Other examples of functional representations may include Wagner's (1989) general model of pleiotropy, Rice's (2002) general mapping models from a set of underlying variables to phenotypes, and Wagner and Stadler's (2003) 'topological' character models. The third representation we may call 'mechanical'. Here genotypes are related to phenotypes through explicit models of developmental or physiological systems. A paradigmatic example is the highly concrete models of tooth development (e.g. Salazar-Ciudad and Järnvall 2004) discussed by Polly, but in this group we may also include more general representations such as models of gene-regulatory networks (e.g. Wagner 1996; Gjuvesland et al. 2007) or metabolic controls systems (e.g. Bagheri et al. 2003).

These representations have different, although overlapping, roles to play in a general theory. In fact, I submit that a successful extension of evolutionary quantitative genetics needs representations of all three types. The statistical representation is necessary for descriptive reasons and for linking to selection. Populations have variation, selection acts on variation, and describing the variation necessitates a statistical model. The functional representation is useful for identifying what structural features of the genotype-phenotype map are important for evolutionary dynamics. The mechanical representations lack generality, but are useful for understanding constraints on specific systems, and may provide ideas, intuition and examples that can form the basis of generalization.

As an example of how functional representations can be used to study the dynamical consequences of genotype-phenotype structure, I present our own recent work on the role of "functional" epistasis in evolutionary dynamics (e.g. Hermisson et al. 2003; Carter et al. 2005; Hansen et al. 2006). Classical quantitative genetics has a statistical representation of epistasis based on a regression model where epistatic interactions implicitly were assumed to be non-directional (i.e. to average to zero). In contrast, a functional representation, in this case the multilinear model of Hansen and Wagner (2001), allows fixed systematic interactions, where gene substitutions may systematically reinforce or diminish the effect of subsequent gene substitutions. This systematic directionality allows for systematic changes in additive effects and will, if present, have strong effects on evolutionary dynamics over anything beyond a handful of generations. These effects were omitted from classical quantitative genetics theory based on a statistical representation of the genotype-phenotype map. The classical epistatic variance components are not just hard to estimate, they are also totally uninformative about evolutionary dynamics, and their use have seriously hampered both theoretical and empirical studies of gene

interaction. In contrast, population parameters measuring patterns of functional epistasis can be highly informative. The evolutionary importance of epistasis should indeed have been obvious from the dynamical effects of functional epistasis in classical two-locus models! Our multilinear extension of evolutionary quantitative genetics tells us that the first step beyond the additive model should be to look for systematic directionality in epistatic interactions. Directional epistasis provides a first approximation to the evolution of evolvability and canalization. Interestingly, these models undermines the notion that we can expect general adaptive changes in evolvability or canalization, because the evolution of gene effects is governed by specific patterns of gene interaction that, for example, may lead to the evolution of reduced evolvability under directional selection (Carter et al. 2005).

Polly (2008) writes of a potential conflict between developmental and evolutionary quantitative genetics models. He points out that many different genotype-phenotype maps can give similar quantitative genetic patterns. Indeed, this is a major insight developed from "functional" representations of pleiotropy in evolutionary quantitative genetics (e.g. Riska 1989; Wagner 1989; Charlesworth 1990; Houle 1991). In particular, Houle's (1991) simple model of functional pathways shows that number of different combinations of acquisition and allocation could generate the same genetic covariances. This precludes direct inference about pleiotropy from patterns of genetic covariance. This does not, however, make the G-matrix uninformative. Any specific model of the genotype-phenotype map, functional or mechanical, will make testable predictions about patterns of segregating variation. Thus, we are simply in the standard situation of testing hypotheses against data, and as usual, there will be alternative hypotheses to explain any given observation. More refined tests of a particular genotype-phenotype map can also be obtained by use of different types of quantitative genetic data including genetic variation in other populations and environments, QTL data, line-cross data, mutation data, and selection-response data. Furthermore, the G-matrices predicted by a given genotype-phenotype map form the link to understand the evolutionary dynamics that can be generated by this map.

It is not correct, however, as Polly makes me (Hansen 2006) say, that the G-matrix adequately accounts for constraints. The G-matrix is an important and perhaps necessary link from genetic variation and variability to evolutionary dynamics, but it is itself an evolvable entity, and understanding its dynamics is therefore essential to achieve an operational macroevolutionary theory for quantitative characters. Hansen (2006) in fact meant to review our current state of knowledge about the evolution of genotype-phenotype maps, and hence indirectly of the evolution of the G-matrix. Its relevance to macroevolution is also underscored by the fact that local estimates of the G-matrix, perhaps surprisingly, seem to correlate with directions of evolutionary change and patterns of among-species variation (see Hansen and Houle 2008 and references therein).

Quantitative genetics presupposes the existence of quantitative characters that are themselves continuous or at least functions of underlying continuous variables. Evolutionary developmental biology has no such restriction, and understanding the origin of novel characters, in the sense of structures that are not even measurable in parts of genotype space, is indeed a major part of its research goals. Polly and others, such as Salazar-Ciudad (2005), see this as a potential conflict between the two fields. While quantitative genetics is certainly not set up to study the emergence of novelty in the strict sense (e.g. Müller and Wagner 1991), I do not see a conflict in using different approaches to study different phenomena. A conflict could arise, however, if different models and assumptions are applied in the same domain of investigation. Polly argues that this could happen if it turns out that developmental models of the genotype-phenotype predict highly qualitative or non-normal patterns of variation.

I think, however, there is less of a potential for conflict than an opportunity for an extended synthesis. The normality assumptions of many quantitative genetics models are not terribly restrictive. First, a normal distribution of the trait can be compatible with even strong non-linearities in the underlying genotype-phenotype map. Normality results from the combination of many quasi-independent factors, and complex, polygenic characters can therefore be expected to be normally distributed, at least after some simple scale transformation. Second, near normality on some easily achievable scale seems to be an empirical fact for most quantitative characters. Third, I suspect a lot of the theory will be rather robust to deviations from normality, which may often just function as an approximation in terms of the first two moments of the trait distribution.

Serious deviations from normality are thus not likely to be common with truly complex, quantitative characters, but may occur in simple genotype-phenotype maps with strong nonlinearities, as for example with threshold characters that may generate bimodal phenotype distributions. Although there exist quantitative genetics models to handle such situations (e.g. Lynch and Walsh 1998, chp. 25), these have not been much investigated from a dynamical perspective, and this is a promising area for theoretical research.

In conclusion, evolutionary quantitative genetics extended with an assortement of explicit genotype-phenotype maps is a promising area for research. We need to develop more models of genotype-phenotype maps, and we need more specific examples for specific organ systems. I stress

the need to explore the evolutionary dynamics that can result from different maps, and to do this, it is particularly important to work with functional representations to achieve an understanding of what structural features are dynamically important. This will tell us what features to look for in the more specific developmental models. So far, we know that additive variance and character autonomy are important, but to build an operational theory of macroevolutionary change, we need to go far beyond that.

References

Alvarez-Castro, J. M., & Carlborg, Ö. (2007). A unified model for functional and statistical epistasis and its application quantitative trait loci analysis. *Genetics, 176*, 1151–1167.

Arnold, S. J., Pfrender, M. E., & Jones, A. G. (2001). The adaptive landscape as a conceptual bridge between micro- and macroevolution. *Genetica, 112/113*, 9–32. doi:10.1023/A:1013373907708.

Bagheri, H. C., Hermisson, J., Vaisnys, J. R., & Wagner, G. P. (2003). Effects of epistasis on phenotypic robustness in metabolic pathways. *Mathematical Biosciences, 184*, 27–51. doi:10.1016/S0025-5564(03)00057-9.

Barton, N. H., & Turelli, M. (2004). Effects of genetic drift on variance components under a general model of epistasis. *Evolution, 58*, 2111–2132.

Bürger, R. (2000). *The mathematical theory of selection, recombination, and mutation*. Chichester: Wiley.

Carter, A. J. R., Hermisson, J., & Hansen, T. F. (2005). The role of epistatic gene interactions in the response to selection and the evolution of evolvability. *Theoretical Population Biology, 68*, 179–196. doi:10.1016/j.tpb.2005.05.002.

Charlesworth, B. (1990). Optimization models, Quantitative genetics, and mutation. *Evolution; International Journal of Organic Evolution, 44*, 520–538. doi:10.2307/2409433.

Cheverud, J. M., & Routman, E. J. (1995). Epistasis and its contribution to genetic variance components. *Genetics, 139*, 1455–1461.

Gjuvsland, A. B., Hayes, B. J., Omholt, S. W., & Carlborg, O. (2007). Statistical epistasis is a generic feature of gene regulatory networks. *Genetics, 175*, 411–420. doi:10.1534/genetics.106.058859.

Hansen, T. F. (2006). The evolution of genetic architecture. *Annual Review of Ecology Evolution and Systematics, 37*, 123–157. doi:10.1146/annurev.ecolsys.37.091305.110224.

Hansen, T. F., Alvarez-Castro, J. M., Carter, A. J. R., Hermisson, J., & Wagner, G. P. (2006). Evolution of genetic architecture under directional selection. *Evolution; International Journal of Organic Evolution, 60*, 1523–1536.

Hansen, T. F., & Houle, D. (2008). Measuring and comparing evolvability and constraint in multivariate characters. *Journal of Evolutionary Biology* (in press).

Hansen, T. F., & Wagner, G. P. (2001). Modeling genetic architecture: A multilinear model of gene interaction. *Theoretical Population Biology, 59*, 61–86. doi:10.1006/tpbi.2000.1508.

Hermisson, J., Hansen, T. F., & Wagner, G. P. (2003). Epistasis in polygenic traits and the evolution of genetic architecture under stabilizing selection. *American Naturalist, 161*, 708–734.

Hill, W. G., Goddard, M. E., & Visscher, P. M. (2008). Data and theory point to mainly additive genetic variance for complex traits. *PLOS Genetics, 4*, 1–10. doi:10.1371/journal.pgen.1000008.

Houle, D. (1991). Genetic covariance of fitness correlates: What genetic correlations are made of and why it matters. *Evolution; International Journal of Organic Evolution, 45*, 630–648. doi:10.2307/2409916.

Houle, D. (2001). Characters as the units of evolutionary change. In G. P. Wagner (Ed.), *The character concept in evolutionary biology* (pp. 109–140). Academic press.

Lande, R. (1979). Quantitative genetic analysis of multivariate evolution, applied to brain:body size allometry. *Evolution; International Journal of Organic Evolution, 33*(1), 402–416. doi:10.2307/2407630.

Lande, R., & Arnold, S. J. (1983). The measurement of selection on correlated characters. *Evolution; International Journal of Organic Evolution, 37*(6), 1210–1226. doi:10.2307/2408842.

Lewontin, R. C. (1974). *The genetic basis of evolutionary change*. Columbia, New York.

Lynch, M., & Walsh, B. (1998). *Genetics and analysis of quantitative characters*. Sinauer.

Müller, G. B., & Wagner, G. P. (1991). Novelty in evolution: Restructuring the concept. *Annual Review of Ecology and Systematics, 22*, 229–256. doi:10.1146/annurev.es.22.110191.001305.

Polly, D. (2008). Developmental dynamics and G-matrices: Can morphometric spaces be used to model phenotypic evolution? *Evolutionary biology, 35*(2), 83–96. doi:10.1007/s11692-008-9020-0.

Rice, S. H. (2002). A general population genetic theory for the evolution of developmental interactions. *Proceedings of the National Academy of Sciences of the United States of America, 99*, 15518–15523. doi:10.1073/pnas.202620999.

Riska, B. (1986). Some models for development, growth, and morphometric correlation. *Evolution; International Journal of Organic Evolution, 40*, 1303–1311. doi:10.2307/2408955.

Riska, B. (1989). Composite traits, selection response, and evolution. *Evolution; International Journal of Organic Evolution, 43*(6), 1172–1191. doi:10.2307/2409355.

Roff, D. A. (2007). A centennial celebration for quantitative genetics. *Evolution; International Journal of Organic Evolution, 61*, 1017–1032. doi:10.1111/j.1558-5646.2007.00100.x.

Salazar-Ciudad, I. (2005). Developmental constraints vs. variational properties: How pattern formation can help to understand evolution and development. *The Journal of Experimental Zoology, 304B*, 1–19.

Salazar-Ciudad, I., & Jernvall, J. (2004). How different types of pattern formation mechanisms affect the evolution of form and development. *Evolution and Development, 6*, 6–16. doi:10.1111/j.1525-142X.2004.04002.x.

Slatkin, M. (1987). Quantitative genetics of heterochrony. *Evolution; International Journal of Organic Evolution, 41*, 799–811. doi:10.2307/2408889.

Wagner, A. (1996). Does evolutionary plasticity evolve? *Evolution; International Journal of Organic Evolution, 50*, 1008–1023. doi:10.2307/2410642.

Wagner, G. P. (1989). Multivariate mutation-selection balance with constrained pleiotropic effects. *Genetics, 122*, 223–234.

Wagner, G. P., & Stadler, P. F. (2003). Quasi-independence, homology and the unity of type: A topological theory of characters. *Journal of Theoretical Biology, 220*, 505–527. doi:10.1006/jtbi.2003.3150.