

# Evolutionary quantitative genetics: Are we in danger of throwing out the baby with the bathwater?

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Quantitative genetics has a long and venerable history: the question I wish to consider in this essay is the future of quantitative genetics. Evolutionary biology, like most fields of science, tends to suffer from a band-wagon effect, which eventually leads to disillusionment and abandonment. The reason for this is that too much is expected of some new or revived area of research. Quantitative genetics as applied to evolutionary biology received a major boost from the extensive work of Lande, who showed how the equations of quantitative genetics could be expanded and applied to problems beyond livestock and crop improvement. This research initiated a flurry of activity in quantitative genetics, both in further theoretical development and empirical determination of genetical parameters such as heritability, evolvability and genetic correlations. This early enthusiasm has largely been expended and there is the risk of quantitative genetics falling on hard times, being considered “old-fashioned” and out-moded in comparison to the new area of molecular genetics. My purpose in this essay is to try to place quantitative genetics in proper perspective, point out that it has had some fabulous successes, and that there are central questions of evolutionary biology that require a quantitative genetic perspective *in conjunction with other modalities of investigation*.

The first achievement of quantitative genetics was the resolution of the debate between the Mendelians and Biometricians. Quantitative

genetic theory is able to account for the inheritance of quantitative traits such as body size, fecundity, etc., within the Mendelian framework. Indeed in many ways Mendelian genetics is really a subset of quantitative genetics rather than vice versa. The units of quantitative genetics are discrete elements, the genes, but the behavior of these elements is considered in the aggregate in the same manner as the properties of a gas are studied as the epiphenomenon of the collection of individual gas molecules. This is not to say that the behavior of individual particles is not of interest or might not be the focus of investigation under some circumstances. Rather, if the question revolves around the epiphenomenon, such as the phenotype then the appropriate scale is beyond the individual elements. One of the areas of growing interest to which I shall return is indeed the dissection of the behavior of these elements at varying levels.

Another significant contribution of quantitative genetics is to an understanding of inbreeding depression. The deleterious effects of inbreeding have been recognized for a considerable amount of time, possibly being the basis of many marriage taboos. It is not *a priori* obvious that for inbreeding depression to occur there must be directional dominance: a trait that shows only additive genetic variation will not suffer inbreeding depression. That this directional dominance can arise from heterozygosity *per se* or deleterious recessives is a corollary of the theory

and has been important in crop improvement (although, because of incorrect interpretation of experiments, heterozygosity rather than deleterious recessives was the mechanism championed for many years; Crow 2000). A further surprise from the theory was that large mutational loads can be carried even in selfing populations (Lande & Schemske 1985), a prediction now well demonstrated (Schemske & Lande 1985, Husband & Schemske 1996). If, as now seems likely, inbreeding depression is due to the exposure of deleterious recessives then further study can usefully combine the quantitative genetic perspective of measuring variation at the level of the whole organism, with a molecular approach designed to isolate those genes producing the deleterious effects. Further, these two levels of investigation can be joined by a study of the intervening mechanism that produces the deleterious effect.

*A priori* one might suppose that selection would be most effective in changing a trait mean if selection operated directly on that trait. The counter-intuitive result of quantitative genetics is that under some circumstances a trait will respond more rapidly if selection acts upon a trait to which the focal trait is genetically correlated (Falconer 1989). Another paradox is that selection can act on a trait that is genetically variable and is genetically correlated with another trait also under selection but produce no response to selection (Roff 2002a: p. 56). Exactly how much genetic architecture constrains evolution is a subject still requiring detailed study. For two traits the answer is simple enough — a genetic correlation of  $\pm 1$  will constrain evolution along a bivariate line. But the answer becomes murky when multiple traits are introduced, particularly when one must consider not simply the restriction that a given optimal combination cannot be achieved but the amount of time required to achieve the optimum. Indeed the question of bivariate evolution is one that casts a shadow over quantitative genetics for it is in this simple area that empirical studies have shown a decided lack of correspondence between theory and observation (Nordskog 1977). This is a subject to which I shall return.

Quantitative genetics in its simplest form takes a strictly statistical approach to variation

decomposing variation into the components of additive, non-additive and environmental variances. Strictly speaking it assumes an infinite number of loci (or alleles) but recognises that in reality each trait is determined by a finite number of loci and alleles. The success of the biometrical viewpoint is that relatively few loci are required to satisfy the statistical requirements of normality. However, it is still important to know how many loci and alleles determine a trait: if there are relatively few contributing factors then selection may quickly run out of steam as variation is eroded. The number of factors has proved to be an elusive quantity to measure (Barton & Turelli 1989) but the developing area of quantitative trait loci (QTL) analysis shows considerable promise in eventually being able to answer this question (for a review of techniques *see* Lynch & Walsh 1998, Mackay 2001). Initial estimates appeared to show that quantitative traits might be controlled by very few genes (Roff 1997), leading to the prospect that we could understand quantitative variation by models that explicitly include all relevant loci. A refinement of techniques has produced more sobering and expected results, with estimates of the number of loci with detectable effects numbering in the hundreds: for example, 276 QTLs for yield in maize (Edwards *et al.* 1987), 137 QTLs for weight in the mouse (Cheverud *et al.* 1996), and over 130 QTLs for bristle number in *Drosophila* (Walsh 2001). These results confirm that for many cases a strictly biometrical approach is appropriate to capture the overall additive effects of genes. However, the new molecular approaches do allow us to address the question of genetic architecture at a level not previously possible. Most importantly, we can begin to study how interactions at the level of the gene manifest themselves as components of variation at the level of the phenotype. Such information will lead to models that connect individual gene action with mass gene action. While such models are technically feasible at present (e.g. Nijhout & Paulsen 1997), the number of possible scenarios is so large that it is far from clear what subset of models should be used: for example, what is the relative importance of epistasis versus dominance, or what role do simple on-off mechanisms of regulation play?

There are a large number of selection experiments on single traits, the sum of which support the general model of quantitative genetics that the response to selection will be proportional to the heritability of the trait. Natural selection does not typically act upon a single trait but upon suites of trait, either directly or indirectly as a consequence of genetic correlation between traits. Although this is a fundamental component of the quantitative genetic model, until recently there were few estimates of genetic correlations relative to heritability estimates. Thus when Tim Mousseau and I (Mousseau & Roff 1987) conducted our review of quantitative genetic parameters we restricted ourselves to heritability estimates for animals in general, because there were too few genetic correlations to adequately analyze for patterns. Our study period finished in 1984, at which time we had 14 studies: by 1996 the number had risen to 68 and an analysis was feasible, which did indeed show that the types of traits involved in the correlation did matter (Roff 1996). The thrust behind the increased estimation of genetic correlations was the then recognized importance of multivariate evolution. But the assumption that, because quantitative genetic theory is able to quite well explain single trait evolution (at least under artificial selection), it can also explain multivariate evolution has not been rigorously tested. The prediction of multi-trait response in a natural population of Darwin's medium ground finch by Grant and Grant (1995) was only partially successful, with a reasonable correlation between prediction and observation during one episode of selection but not another (Roff 1997). Artificial selection on two traits simultaneously has shown that there is something amiss with the simple model of quantitative genetics. When selection is reinforcing and correlations are large (as with the ground finch) the multivariate responses are typically more or less as expected. But when selection is antagonistic the responses are frequently quite erratic, leading Nordskog (1977) to opine "current quantitative genetic theory seems not to be of help in this case". Unfortunately, the experiments on two-trait selection have not been carried out with the aim of actually discovering why there are so many failures of prediction. A much needed area of study is in the causes of the erratic responses

to two-trait selection from both a theoretical perspective (e.g. Turelli & Barton 1990, Reeve 2000) and by more intensive experimental study. Such a study would involve not simply deriving genetic parameters but ultimately examining the mechanistic basis for the observed responses to selection. Given the importance of multivariate evolution, such experiments would seem to be of fundamental significance both from the viewpoint of better quantitative genetic models and to understand constraints on evolutionary change.

Two principle components in modeling multivariate evolution are the phenotypic and genetic variance-covariance matrices (hereafter, **P** and **G** matrices, respectively). It would certainly be convenient if these matrices did not change. While the argument of selection-mutation balance can be advanced in support of such an assumption (Via & Lande 1985), it requires empirical verification (Turelli 1988), which at this time is lacking. At some taxonomic level variation is to be expected but at present there are too few estimates to determine a consistent pattern and no theory that gives us a guide to when we might expect significant differentiation. The estimation of **G** matrices is a daunting task even for morphological traits for which full sib estimates will generally suffice: for life history traits, where large non-additive effects might be expected, the necessary half-sib or offspring-parent approaches present a very serious challenge. Because they are so much easier to estimate accurately, if one could use the **P** matrices as a surrogate for the **G** matrix considerable advances could be made. The presence of non-additive effects in life history traits precludes this approach for these traits but it a reasonable approach for morphological traits, and most multi-taxon comparisons have used this surrogate measure (Steppan *et al.* 2002). Thus far, too few studies have been published to draw general patterns but these studies make it clear that combining matrix comparison with phylogenetic comparison is a fruitful approach. Additionally, the correlation between matrix variation and other variables such as ecological, geographical or life historical is important in providing a foundation upon which theory can be developed (Roff 2002, Roff *et al.* 2004). The technical difficulties of estimating **G** matrices for life history

traits might prevent substantial progress in this area, although the use of this technique on clonal species could be productive.

There is considerable concern for the loss of biodiversity. The probability of extinction is a function of population size and reduced genetic variation. Molecular markers can be used to study patterns of migration among populations and to differentiate among populations and species but can such markers identify the likelihood of loss of genetic variance in traits of ecological significance? The answer to this comes in two parts: first, at best the correlation between molecular diversity (heterozygosity) and quantitative genetic variation (e.g. heritability) is weak, with molecular measure explaining only about 4% of the variation in quantitative traits (Reed & Frankham 2001). Therefore, the potential for evolutionary response in quantitative traits cannot be predicted by use of molecular measure, and thus there remains a central place for quantitative genetic analysis in the assessment of the extinction risk in conservation biology. The second part of the answer concerns the relative roles of selection and drift in causing differentiation among populations. Here a meta-analysis found that the molecular measure of population differentiation,  $F_{ST}$  was typically less than the quantitative genetic measure of divergence,  $Q_{ST}$ , but that the two were correlated (Merilä & Crnokrak 2001). The former finding implies that directional selection is driving populations apart, while the latter suggests that molecular markers can be used as an index of the degree of differentiation in quantitative traits. A further review by McKay and Latta (2002) challenged the second finding, leading to a lively debate (Crnokrak & Merilä 2002, Latta & McKay 2002, Hendry 2002), which requires further theoretical and empirical study to fully resolve. The importance of the issue is that the reconstitution of endangered populations by the introduction of individuals that are poorly adapted to the new local environment could actually lead to an increased probability of extinction rather than rescue.

The ultimate source of variation is mutation, which in artificial selection experiments can substantially increase the long-term response (Hill & Mbagha Said 1998), and may play a pivotal role in the maintenance of quantitative genetic

variation in populations (Burger 1998, Houle 1998, Lynch *et al.* 1998). Analysis of the effects of multiple mutations on quantitative genetic variation requires a biometrical approach (e.g. Houle 1998, Kondrashov 1998). In the ideal world each mutation could be located and its separate effects studied by manipulation of the genetic background. But even in such a world we would still need to combine all these effects into some aggregated distribution of effects. Thus such a study would combine the fine-scale analysis of molecular genetics with the "global" perspective of quantitative genetics.

A central question in evolutionary biology is how so much genetic variation can be maintained in populations. There are a number of contending hypotheses: mutation-selection balance, heterozygous advantage, antagonistic pleiotropy, frequency-dependent selection, and environmental heterogeneity. Mutation-selection balance has a very firm theoretical foundation (Roff 1997: pp. 355–363, Burger 1998) but empirical estimates of the necessary mutational parameters are still very poorly estimated (Garcia-Dorado *et al.* 1998, Lynch *et al.* 1998). The other hypotheses have each been explored theoretically and each is a plausible hypothesis but, as with mutation-selection balance there is a dearth of empirical investigations. Perhaps more significantly, there has been no study of how one would actually distinguish among these hypotheses. So, for example, the antagonistic pleiotropy hypothesis requires a minimum level of dominance variance, though the actual required ratio of additive to dominance variance is still largely unknown. But suppose we knew this ratio and were able to demonstrate that for two particular traits this ratio was exceeded. Would this mean that genetic variance in these traits is maintained by antagonistic pleiotropy? No, it would only mean that antagonistic pleiotropy could not be discounted. It is not a stretch to say that at present we have no idea how to compare the competing hypotheses and that we are still woefully ignorant as to the primary mechanism, should one exist, that maintains genetic variance within populations. Yet this standing variation is the very essence of evolutionary change

Quantitative genetics is not dead or moribund, but it is, I think, misunderstood. It is part

of the arsenal of tools that we have to measure and dissect evolutionary change. It was developed in an era when mathematical analysis was greatly impeded by the lack of computing power. It was, partly at least, for this reason that several important simplifying assumptions were made. For example, epistasis and maternal effects were largely “swept under the rug” as being mathematical inconveniences: we now recognize them as important contributors to evolutionary change (Mousseau & Fox 1998, Wolf *et al.* 2000) and their incorporation into a grander quantitative genetic framework should enable more detailed examination of their importance. In like manner the importance of conversion of non-additive to additive genetic variance when populations pass through bottlenecks is of both theoretical importance and of practical interest to conservation biologists. Molecular biology is making extraordinary strides in locating genes that have major effects: quantitative genetics is a means by which the aggregate properties of genes of both major and minor effect can be understood. Any theory that is developed from the gene up must be capable of reproducing those phenomenon predicted and measured by quantitative genetic theory and application. We do not need more estimates of heritability, evolvability or **G** matrices but we do need more studies of how these central components of evolution change over time: what part does mutation play, what part does drift play, what part does selection play, what part do constraints (physiological, mechanical, ecological etc) play?

## References

- Barton, N. H. & Turelli, M. 1989: Evolutionary quantitative genetics: how little do we know? — *Annu. Rev. Genet.* 23: 337–370.
- Burger, R. 1998: Mathematical properties of mutation-selection models. — *Genetica* 102/103: 279–298.
- Cheverud, J. M., Routman, E. J., Duarte, F. A. M., van Swinderen, B., Cothran, K. & Perel, C. 1996: Quantitative trait loci for murine growth. — *Genetics* 141: 1305–1319.
- Crnokrak, P. & Merilä, J. 2002: Genetic population divergence: Markers and traits. — *Trends Ecol. Evol.* 17: 501.
- Crow, J. F. 2000: The rise and fall of overdominance. — *Plant Breeding Reviews* 17: 225–257.
- Edwards, M. D., Stuber, C. W. & Wendel, J. F. 1987: Molecular-marker-facilitated investigations of quantitative-trait loci in maize. I. Numbers, genomic distribution and types of gene action. — *Genetics* 116: 113–125.
- Falconer, D. S. 1989: *Introduction to quantitative genetics*. — Longman, New York.
- Garcia-Dorado, A., Monedero Juan, L. & Lopez-Fanjul, C. 1998: The mutation rate and the distribution of mutational effects of viability and fitness in *Drosophila melanogaster*. — *Genetica (Dordrecht)* 102/103: 255–265.
- Grant, P. R. & Grant, B. R. 1995: Predicting microevolutionary responses to directional selection on heritable variation. — *Evolution* 49: 241–251.
- Hendry, A. P. 2002: QST ≥ FST? — *Trends in Ecology & Evolution* 17: 502.
- Hill, W. G. & Mbaga Said, H. 1998: Mutation and conflicts between artificial and natural selection for quantitative traits. — *Genetica (Dordrecht)* 102/103: 171–181.
- Houle, D. 1998: How should we explain variation in the genetic variance of traits? — *Genetica (Dordrecht)* 102/103: 241–253.
- Husband, B. C. & Schemske, D. W. 1996: Evolution of the magnitude and timing of inbreeding depression in plants. — *Evolution* 50: 54–70.
- Kondrashov, A. S. 1998: Measuring spontaneous deleterious mutation process. — *Genetica (Dordrecht)* 102/103: 183–197.
- Lande, R. & Schemske, D. W. 1985: The evolution of self-fertilization and inbreeding depression in plants. I. Genetic models. — *Evolution* 39: 24–40.
- Latta, R. G. & McKay, J. K. 2002: Genetic population divergence: Markers and traits: Response from Latta and McKay. — *Trends Ecol. Evol.* 17: 501–502.
- Lynch, M., Latta, L., Hicks, J. & Giorgianni, M. 1998: Mutation, selection, and the maintenance of life-history variation in a natural population. — *Evolution* 52: 727–733.
- Lynch, M. & Walsh, B. 1998: *Genetics and analysis of quantitative traits*. — Sinauer Associates, Sunderland, MA.
- Mackay, T. F. C. 2001: The genetic architecture of quantitative traits. — *Annu. Rev. Genetics* 35: 303–339.
- McKay, J. K. & Latta, R. G. 2002: Adaptive population divergence: Markers, QTL and traits. — *Trends Ecol. Evol.* 17: 285–291.
- Merilä, J. & Crnokrak, P. 2001: Comparison of genetic differentiation at marker loci and quantitative traits. — *J. Evol. Biol.* 14: 892–903.
- Mousseau, T. & Fox, C. W. (eds.) 1998: *Maternal effects as adaptations*. — Oxford Univ. Press, New York.
- Mousseau, T. A. & Roff, D. A. 1987: Natural selection and the heritability of fitness components. — *Heredity* 59: 181–198.
- Nijhout, H. & Paulsen, S. M. 1997: Developmental models and polygenic characters. — *Am. Nat.* 149: 394–405.
- Nordskog, A. W. 1977: Success and failure of quantitative genetic theory in poultry. — In: Pollack, E., Kempthorne, O. & Bailey, T. B. (eds.), *Proceedings of the International Conference on Quantitative Genetics*: 569–586. Iowa State University Press, Iowa.
- Reed, D. H. & Frankham, R. 2001: How closely correlated are molecular and quantitative measures of genetic variation? A meta-analysis. — *Evolution* 55: 1095–1103.

- Reeve, J. P. 2000: Predicting long-term response to selection. — *Genet. Res.* 75: 83–94.
- Roff, D. A. 1996: The evolution of genetic correlations: an analysis of patterns. — *Evolution* 50: 1392–1403.
- Roff, D. A. 1997: *Evolutionary quantitative genetics*. — Chapman and Hall, New York.
- Roff, D. A. 2002b: Comparing G matrices: a MANOVA method. — *Evolution* 56: 1286–1291.
- Roff, D. A. 2002a: *Life history evolution*. — Sinauer Associates, Sunderland, MA.
- Roff, D. A., Mousseau, T., Møller, A. P., de Lope, F., & Saino, N. 2004: Geographic variation in the G matrices of wild populations of the barn swallow. — *Heredity*. [In press].
- Schemske, D. W. & Lande, R. 1985: The evolution of self-fertilization and inbreeding depression in plants. II. Empirical observations. — *Evolution* 39: 41–52.
- Steppan, S. J., Phillips, P. C. & Houle, D. 2002: Comparative quantitative genetics: Evolution of the G matrix. — *Trends Ecol. Evol.* 17: 320–327.
- Turelli, M. 1988: Phenotypic evolution, constant covariance, and the maintenance of additive variance. — *Evolution* 42: 1342–1347.
- Turelli, M. & Barton, N. H. 1990: Dynamics of polygenic characters under selection. — *Theor. Pop. Biol.* 38: 1–57.
- Via, S. & Lande, R. 1985: Genotype-environment interaction and the evolution of phenotypic plasticity. — *Evolution* 39: 505–522.
- Walsh, B. 2001: Quantitative genetics in the age of genomics. — *Theor. Pop. Biol.* 59: 175–184.
- Wolf, J. B., Brodie, E. D. I. & Wade, M. J. 2000: *Epistasis and the evolutionary process*. — Oxford Univ. Press, New York.