What maintains genetic variation in natural populations? A commentary on 'The maintenance of genetic variability by mutation in a polygenic character with linked loci' by Russell Lande

PATRICK C. PHILLIPS*

Center for Ecology and Evolutionary Biology, University of Oregon, Eugene, OR 97403, USA

The 'Chicago School' of quantitative genetics that dominated much of evolutionary thinking in the later part of the twentieth century had its genesis at Harvard in the early 1970s. It was during this time as a graduate student in Richard Lewontin's laboratory that Russ Lande began a series of papers that would end up shaping much of the way we think about the evolution of complex traits. Lande began his graduate career with an interest in theoretical ecology but was soon motivated to translate G. G. Simpson's ideas about large-scale patterns in evolution into the formalism of population genetics developed by Sewall Wright. The merging of these approaches found their nexus in quantitative genetics, which allowed Lande to precisely formulate equations for evolutionary change in a way that made it possible to challenge his theoretical results with empirical data. In two parallel sets of papers, Lande laid out the theory of the response to selection and the maintenance of genetic variation for both single traits (Lande, 1976 *a*, *b*) and for suites of correlated characters (Lande, 1979, 1980, 1984), with the former forming the core of his dissertation work. Together with his and Steve Arnold's work on the analysis of selection (Lande & Arnold, 1983), this theory provides a coherent system for understanding the evolution of traits whose patterns of variance and covariance are stable enough that the precise genetic details underlying this variation can essentially be ignored. The conditions under which this kind of abstraction is possible is part of the focus of Lande's seminal paper in *Genetical Research* published in 1976 (Lande, 1976 *a*).

Lande (1976 *a*) is concerned with one of the central questions in evolutionary genetics: How is genetic variation maintained within natural populations? Lande notes that, prior to his work, mutation was thought to be insufficient to explain the high levels of genetic variation seen for many traits, yet most of the common models used to explain the maintenance of genetic variation under selection, such as overdominance or heterozygote advantage, lacked empirical support. However, the seemingly limited role for mutation might have been caused by the fact that computational difficulties had previously made it difficult to study the influence of many loci acting simultaneously. One of Lande's major contributions here was therefore developing a system for tracking the contributions of many, potentially linked, loci to the maintenance of genetic variation.

To pull this off, Lande began with two basic premises. Firstly, he assumed that traits that are not directly tied to fitness are likely to be under stabilizing selection, which Lande approximated using a fitness surface shaped like normal or Gaussian distribution. Secondly, and this is the more contentious issue, Lande assumed that the distribution of allelic effects segregating at each locus is multivariate normal (the multivariate part coming from the fact that linkage can generate gametic correlations between the effects of different loci). If these two relationships hold true, then the fact that convolution (or mixing) of two multivariate normal distributions is also normal can be used to solve the very difficult problem of finding the equilibrium level of genetic variation segregating within a population. The math used in this paper can be somewhat daunting to the non-expert, but it essentially comes down to following what happens when multiple normal distributions (allelic, phenotypic and selective) are combined with one another (see e.g. eqns 7–10). The result ends up being dependent on the sum of the 'variances' from each of the sources (w^2 for fitness, σ_e^2 for the environmental component of the phenotypic variance, and $\mu_i m_i^2$ for the mutational effects), which results in the fundamental result presented in eqn (21c).

Equally influential as the mathematical work is Lande's attempt to ground these theoretical results with empirical estimates of mutational processes. From these estimates, Lande concludes that it is realistic to think that 'mutation can be a potent force maintaining genetic variation in polygenic characters under stabilizing selection' (p. 233). Looking back

* e-mail: pphil@uoregon.edu

over three decades, is this a robust conclusion? The fact is that we still do not know.

Lande pointed out that the Gaussian assumption would only hold up if the effects of new mutations are much smaller than standing allelic variation. When this is not true, Turelli (1984) showed that for both continuous and discrete models of allelic variation, standing levels of genetic variation are better described by a 'house of cards' model in which new mutations strongly disrupt the genetic background within which they arise. The basic problem here is that per-locus mutation rates are thought to be too low to allow the Gaussian model to hold unless the number of loci affecting traits is very large, but the mutation rate data suggest that the effects of mutations must be generally larger than standing variation to explain most heritability estimates. An obvious conclusion might therefore be that mutation–selection balance is not the only thing determining levels of standing variation within natural populations, but this note is not the place to go into those arguments (see Barton & Keightley, 2002, and Johnson & Barton, 2005, for reviews).

There is currently a big push to identify the genes underlying quantitative characters, and indeed this is one of the missions of the journal that now inherits the mantle from *Genetical Research*. From an evolutionary perspective, why is this better than measuring heritabilities and genetic correlations? As has become clear from the sophisticated multilocus models that have been developed following Lande's work (e.g. Barton & Turelli, 1987, 1991), at least part of the answer is that we need to know the distribution of mutational effects underlying genetic variation in order to know whether the assumptions that Lande makes hold water or whether higher moments, such as mutational skewness, are large enough to invalidate global statements regarding the long-term stability of quantitative genetic parameters. Addressing these questions does not actually appear to be a motivating factor in most quantitative trait locus (QTL) studies, however, and we are obviously still very far away from rigorously addressing these hypotheses, because

mutation itself is extremely difficult to study (Mitchell-Olds *et al.*, 2007). It is one thing to identify alleles fixed between two divergent populations, but quite another to measure the distribution of allelic effects at that locus. Thus, despite some conceptual advances, it appears that we are quite far from having the empirical data necessary to adequately address the questions raised by Lande in this paper. There is much work yet to do.

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