ON THE LIMITS OF QUANTITATIVE GENETICS FOR THE STUDY OF PHENOTYPIC EVOLUTION

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ABSTRACT

During the last two decades the role of quantitative genetics in evolutionary theory has expanded considerably. Quantitative genetic-based models addressing long term phenotypic evolution, evolution in multiple environments (phenotypic plasticity) and evolution of ontogenies (developmental trajectories) have been proposed. Yet, the mathematical foundations of quantitative genetics were laid with a very different set of problems in mind (mostly the prediction of short term responses to artificial selection), and at a time in which any details of the genetic machinery were virtually unknown. In this paper we discuss what a model is in population biology, and what kind of model we need in order to address the complexities of phenotypic evolution. We review the assumptions of quantitative genetics and its most recent accomplishments, together with the limitations that such assumptions impose on the modelling of some aspects of phenotypic evolution. We also discuss three alternative approaches to the theoretical description of evolutionary trajectories (nonlinear dynamics, complexity theory and optimization theory), and their respective advantages and limitations. We conclude by calling for a new theoretical synthesis, including quantitative genetics and not necessarily limited to the other approaches here discussed.

"In any case in which the Guide and reality are at odds, it is reality that is wrong"
(Douglas Adams, "*The Hitchhiker's Guide to the Galaxy*")

1. HISTORICAL PROLOGUE

Modern evolutionary biologists (e.g., Mayr and Provine, 1980; Futuyma, 1986; Hartl & Clark, 1989; Barton, 1992; Willis & Orr, 1993), recognize two contrasting 20th century views of biological evolution and its genetic basis: one based on Fisher's 'fundamental theorem of natural selection' (Fisher, 1930), the other revolving around Wright's ideas of 'universal pleiotropy' and evolution on 'multiple adaptive peaks' (Wright, 1931, 1980). Fisher envisioned phenotypes as determined mostly by polygenic inheritance, with many

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loci characterized by small and additive effects controlling each trait. Evolution would happen gradually, primarily in large populations, and would eventually lead to a single equilibrium representing the state of maximum fitness. At that point, by definition, there would be no genetic variation for traits associated with fitness. Fisher had previously developed an entirely new and powerful statistical technique based on these assumptions: the analysis of variance. He had also originated the field of quantitative genetics as we know it today. Wright believed, on the other hand, that phenotypes are controlled by complex interactions between genes and that many genes have major effects on character expression. Wright saw evolution as happening mostly in small and peripheral populations, subject to rapid accelerations and constant turmoil, capable of moving toward multiple adaptive peaks in a complex and ever-changing fitness landscape. Wright also left a legacy of mathematical tools based on his world view, most notably multivariate techniques such as factor and path analyses.

In light of this historical course of ideas, of the fact that Fisher's view has dominated the evolutionary synthesis, and of the current state of the art of studies and models of phenotypic evolution, the scope of this note includes: *(i)* a discussion of the purposes, advantages and limitations of models in evolutionary biology; *(ii)* a brief review of the foundations and assumptions of quantitative genetics, the major 'Fisherian' tool used by current evolutionary theorists; *(iii)* a summary of recent advances in quantitative genetics that expand on its classical applications, to include evolution of phenotypic plasticity and of developmental trajectories; *(iv)* the recognition of the limits of quantitative genetics in relation to the kinds of models necessary for describing phenotypic evolution; and *(v)* a discussion of possible alternative or complementary approaches to quantitative genetics for modelling phenotypic evolution.

We feel compelled to warn the reader that our representation of quantitative genetics may come across as simplistic. However, our goal is to identify the fundamental aspects of the discipline, its bottom-line assumptions and the way these are used in practice. It can of course be argued that theoretical quantitative geneticists are well aware of the limitations of their models, or that some problems can in principle be accommodated by including additional terms in the standard equations describing evolution of phenotypes and genetic variance-covariances. But, if an awareness of the limits of the quantitative genetic approach is not accompanied by prudent applications of its statistical tools, or if enhancements of the current theoretical structure are impossible to implement or test in laboratory or field experiments, then we believe that a critique of the baselines of the theory and of our common objectives as evolutionary biologists is in order. Our hope in writing this paper is to stimulate an open and frank debate, not a sterile clash between defenders and opponents of the current status quo.

2. EPISTEMOLOGY: WHAT IS A MODEL?

According to the Oxford Dictionary, a model is 'a simplified description of a system for calculations'. Useful models lie in a poorly defined zone between two extremes. As an example, consider a topographic map as a model of a territory. At one end, the map can be greatly simplified to include only a few symbols indicating major roads and geological features. Although quite simple to understand for the user, such a model is unlikely to yield any valuable information or insight about the actual complexity of the area. At the opposite

end, the map could be a 1:1 representation of the topography to be studied. This would certainly be a very realistic model, but no more useful than actually visiting the site and finding your way around directly. It is clear that there is no such thing as the 'best' model for our territory. Various maps, characterized by different scales, levels of detail or emphasis on particular aspects of the area, will be equally valuable models, depending on what questions we wish to answer (Oreskes *et al.*, 1994). Another point to make clear is that models cannot be 'wrong': unless the mathematics on which they are based is flawed, a model's conclusions will be consistent with that model's assumptions. If the predictions thus derived are at odds with biological reality, then either some of the assumptions should be questioned, or the model has omitted some crucial aspect of reality.

In science, and in evolutionary biology in particular, a model has two functions: one explanatory, the other predictive. *(i)* The explanatory function is to summarize the important details of the system under study. It is a way to synthesize, in a formal and testable way, the fundamental aspects of biological complexity. This is also one of the basic objectives of science: to derive universal generalizations from a seemingly disparate collection of facts. Several models can equally well summarize the characteristics of a system: for example, if we consider the movement of a projectile at subluminal speed and in the absence of friction, both Newton's mechanics and Einstein's relativity can explain all the data that an experimenter can gather. Based on this, there is no logical way to prefer one model over another, except to invoke Occam's razor: the simplest explanation (in this case, Newton's theory) is considered more elegant or probable. *(ii)* The predictive function consists of the ability of the model to guide future research, leading to the discovery of novel phenomena, and eventually to the formulation of a new model as a result of our changed view of the world. In our example, Newtonian mechanics is not able to predict the complex phenomena associated with projectiles that move at velocities close to that of light (such as particles produced in subatomic physics experiments, or gases ejected from the nuclei of certain galaxies). While Newton's theory is falsified by these empirical results, the same data confirm Einstein's view. This game of falsification and confirmation is at the centre of the evolution of scientific theories (Lakatos, 1974).

Should we conclude that Newton's mechanics has to be abandoned in favour of Einstein's relativity? It depends on our objectives. If the objective is to design a general theory of the physical properties of our universe, or to push the cutting edge of experimental physics and astronomy, the answer is yes. But if we want reasonably accurate predictions about the flight of an airplane or the trajectory of a cannon ball, then it is unnecessary to use relativity: not only would the calculations be cumbersome, but the precision of the predictions would be no better for practical purposes than those yielded by Newton's model. In conclusion, *some models find their realm of application in basic science, but others, not adequate for such purposes, may be more practical for use under different circumstances.* Let us not confuse the map (and its usefulness) with the territory (and its complexity).

3. QUANTITATIVE GENETICS: FOUNDATIONS AND ASSUMPTIONS

Quantitative genetics is a statistical description of the evolution of phenotypes. Quantitative genetic models, although based on a particular mechanistic description of phenotypic traits (see below), are capable of accommodating almost any alternative, as long

as they do not grossly violate some fundamental assumptions. This is usually acknowledged by stating that quantitative genetics treats the underlying genetic control of a phenotype as a 'black box', and is limited to describing its statistical properties. In this sense, quantitative genetics is akin to classical thermodynamics in physics: regardless of the details of the kinetics of gas particles, if they can be collectively described as governed by Brownian motion, then it is possible to predict the behaviour of the gas *at or near equilibrium* (i.e., when the assumptions hold). The parallel between quantitative genetics and thermodynamics is both historical and methodological. Both were proposed as general statistical theories to describe complex systems close to equilibrium (which in the case of many quantitative genetic models is represented by the assumption of weak stabilizing selection as the main evolutionary force acting on a population). Both are based on similar sets of assumptions, rely on linear mathematics, and are proposed as 'first approximations' to real systems. Furthermore, Fisher consciously modelled his fundamental theorem on the second law of thermodynamics (Provine, 1971): the objective was to provide as simple a formula as possible capable of explaining crucial aspects of biological reality.

What are the fundamental assumptions of quantitative genetic models? *(i) Linearity.* Genetic and environmental effects on phenotypes are expected to be described by linear functions. The analysis of variance, the heart of the statistical treatment of quantitative genetics, is a special case of the so-called general linear model. The justifications for the use of linear mathematics are that: (a) it is analytically tractable (most nonlinear equations do not have general solutions) and (b) it yields results intuitively understandable by the user (the biological interpretation of nonlinear terms in models is often open to discussion or completely unclear). *(ii) Additivity.* The assumption of additivity amounts to the relegation of any interaction - among genes (epistasis) or between genes and environments (G x E) - to a minor role. In fact, it is the presence of interactions that causes deviations from additivity. Interactions can be detected by an analysis of variance, but only as residual variances not explained by the major additive effects (Lewontin, 1974). The general justifications for adopting this approach are that: (a) it often turns out that non-additive effects (and non-linear ones) explain only a tiny portion of the total variance. (We note, however, that quantitative genetic experimental designs are not usually able to distinguish between nonlinear and non-additive effects, and these are lumped into the general category of 'interaction' terms.); (b) it is only the additive genetic variance that can respond to selection (holds completely only when there is random mating: if the organism propagates at least partially via vegetative or clonal, reproduction, or if it is partially selfing, then both additive and non-additive genetic variances may respond to selection; see Ebert *et al.*, 1993). A more subtle distinction is also to be made between *statistical* and *biological* additivity. Strictly speaking, quantitative genetics methods only require statistical additivity, which can hold even if there is dominance or epistasis at the gene level. However, the theory was originally built upon the assumption of biological additivity of allelic effects. To uncouple the two is equivalent to make quantitative genetics a 'black box' approach, insensitive to the details of the genetic machinery. *(iii) Normality.* The description of univariate or multivariate (Lande, 1979; Lande & Arnold, 1983) evolution is easily accomplished if the genetic effects follow a (multi-) normal distribution, or if selection is extremely weak. This is because the fundamental parameters in quantitative genetic models are variances and covariances, quantities defined by precise properties within the context of normality, and that may be dramatically distorted by strong selection. *(v) Constancy of the fitness landscape.* As evidenced by Wilkinson *et al.* (1990), quantitative genetic

predictions are based on the constancy of the fitness landscape (i.e., the multidimensional space relating phenotypes to fitness). This is equivalent to ignoring frequency-dependent selection or any other phenomenon (such as changes in the abiotic environment) that would alter, through time, the relationships between character states and fitness values. *(vi) Constancy of the genetic variance-covariance matrix.* The matrix describing the genetic variances and covariances between different traits (G) is fundamental to predictions of evolutionary trajectories. Its use assumes that either (a) there is a one-to-one relationship between genetic mechanisms and their statistical description offered by the matrix (so that it is possible to infer processes from patterns); or (b) the mechanistic basis of heredity is irrelevant to the statistical properties of the model. G is usually assumed to be constant or almost constant over evolutionary time, thereby greatly simplifying the dynamics of evolutionary trajectories (for discussion see Gavrilets and Hastings, 1995). *(vii) Search for equilibria.* Although this is not strictly an assumption of quantitative genetics (van Tienderen, 1991; Gomulkiewicz & Kirkpatrick, 1992; Kirkpatrick & Lofsvold, 1992; Via & Lande, 1985, 1987), it follows from the attributes of quantitative genetic models that we have already discussed: (a) the use of linear dynamics: systems of equations describing long-term phenotypic evolution are solvable, with the object being to find the conditions for the final equilibrium; (b) the underlying assumption that the environment is not changing (or is alternating in fixed proportions: Via, 1987); (c) the constancy of the fitness landscape; and (d) the constancy of the genetic variance-covariance matrix.

Quantitative genetics has been used for almost a century as a model for both the description and the prediction of evolutionary change, induced by either artificial or natural selection. According to the current paradigm, the description relies on the properties of the G matrix and on the estimation of the variance-covariance matrix from analyses of variance. Quantitative genetics has been employed for prediction of both short and long term evolutionary trajectories. (a) Short term evolution. Most of the theory and practice of quantitative genetics originally developed from animal and plant breeding programs. The prediction of short term evolution under either artificial or natural selection is one of the crowning achievements of quantitative genetics, documented in a multitude of projects on a wide array of organisms (Falconer, 1989). (b) Long term evolution. Quantitative genetics has been applied only recently to the prediction of long-term evolutionary change, where its characteristic equations are iterated for hundreds or thousands of generations.

4. THE EXPANSION OF QUANTITATIVE GENETICS: EVOLUTION OF PLASTICITY AND ONTOGENY

Recent papers extended the quantitative genetics approach to include two major topics missing from the classical theory: the evolution of phenotypic plasticity and of ontogenetic trajectories. This followed what can be considered the major breakthrough of quantitative genetics after the foundations laid by Fisher, the treatment of multivariate evolution (Lande, 1979; following Young & Weiler, 1960).

(i) Evolution of plasticity. The first paper to address phenotypic plasticity as an evolving character within a quantitative genetics framework was published by Via and Lande (1985). They made use of Falconer's suggestion (1952) of treating the expression of one character in two (or more) environments as two (or more) distinct characters related in the form of a (cross-environment) genetic correlation. This immediately lent itself to the use of the same

type of equations that Lande (1979) devised for the evolution of multiple traits in one environment. One of the major findings of this approach (Via, 1987) was that even slightly negative genetic correlations could dramatically constrain (and eventually halt altogether) phenotypic adaptation to multiple environments. To be precise, an average genetic correlation among traits/environments of $r_g = |1/n|$ (where n is the number of traits/environments) would prevent any evolution towards a multivariate optimum. In the absence of such a constraint, populations are expected to reach a final optimal equilibrium with a single plastic genotype, unless there is a cost to plasticity (van Tienderen, 1991). Gillespie & Turelli (1989), however, argued that Via's conclusion is based on the empirically unlikely assumption that one reaction norm in the population would be 'superior' under all environments. They show that plasticity can still maintain substantial genetic variation at equilibrium with heterozygote advantage in multiple environments. Schlichting and Pigliucci (1993) have argued that the same result can be reached when there is substantial Genotype by Environment interaction due to non-additive genetic effects.

van Tienderen (1991) addressed the question of costs under regimes of soft and hard selection in coarse-grained environments. He found that under soft selection there is a single adaptive peak and the population evolves towards it, until the equilibrium mean is a compromise reaction norm, depending on both the frequency of the alternative environments and the cost of maintaining a generalist strategy. Under hard selection, however, the dynamics are qualitatively different: there are multiple peaks, and the final outcome depends on the initial conditions (i.e., it is influenced by the past history of the population). Gomulkiewicz and Kirkpatrick (1992) further extended the quantitative genetics approach, considering continuous (instead of discrete) environments (the so-called 'infinite-dimensional' model). They found that (even when selection favours the same reaction norm) the evolutionary outcomes and trajectories strongly depend on the form of environmental variation (hard vs. soft selection, spatial vs. temporal heterogeneity). The final equilibrium is also influenced by the pattern of genetic variation for the reaction norms, and by the interaction between this pattern and the form of environmental variation. A similar approach has been independently formulated by Gavrilets and Scheiner (1993). Their model predicts that the favoured genotype is that which maximizes the mean geometric fitness over all environments, and that a linear reaction norm would evolve under most conditions, even when nonlinear norms are possible. de Jong (1990) also developed a quantitative genetic model for the evolution of reaction norms, starting from the special case of two loci and generalizing to polygenically determined norms. One of her most important conclusions is that developmental constraints (in the form of pleiotropic effects) may prevent additive genetic covariance from changing sign, thereby limiting phenotypic evolution in multiple environments.

(ii) Evolution of ontogeny. In recent years, several attempts to include developmental biology in quantitative genetics have been published (e.g., Cheverud *et al.*, 1983; Atchley, 1987; Slatkin, 1987). The most comprehensive effort is probably that of Atchley and Hall (1991), using a combination of analysis of variance and path analysis in a model that includes maternal and epigenetic components of phenotypic variation. Atchley and Hall, however, admit that their ANOVA models are so complex to preclude the detection or estimation of all sources of variation in a single experiment. An infinite-dimensional model to describe selection and constraints on the evolution of ontogenetic trajectories has been proposed by Kirkpatrick and Lofsvold (1992). One of their major conclusions is that - due

to genetic correlations among the same trait expressed at different ages (i.e., an approach analogous to the one used by Via and Lande to model the same trait in multiple environments) - evolution may alter the height of the trajectory, but not its shape, even after 10,000 generations of selection. Such a result is at odds with real populations and species, as any developmental biologist could testify to the fact that ontogenetic trajectories of closely related species may differ dramatically in shape as well as height (Gould, 1977).

5. WHAT TYPE OF SYSTEM DO WE WISH TO MODEL?

Several authors have pointed out some of the problems or limitations of quantitative genetics as a general framework for modelling phenotypic evolution (e.g.: Lewontin, 1974; Gupta & Lewontin, 1982; Turelli, 1988; Barton & Turelli, 1989; Riska, 1989; Wilkinson *et al.*, 1990; Schlichting & Pigliucci, 1993, 1995). We will now explore the experimental and theoretical problems of quantitative genetics predictions. We will try to define what kind of details we should aim at modelling, given our current knowledge of biological systems.

(i) Molecular genetics and the quest for the mechanistic basis of phenotypes. A 'black box' approach to the genetic determination of phenotypes could certainly be justified when Fisher laid the foundations of modern quantitative genetics. Not only did we not have any idea of the mechanistic details of gene action, we did not even know what a gene was made of. The molecular biology revolution, however, has provided an abundance of experimental systems that should allow us to 'open the box', and to construct models that include more biologically realistic details than ever before (Pigliucci, 1996). The mechanisms of genetic control of bacterial operons, allosteric enzymes, environmentally mediated genetic switches, hierarchical gene regulation, homeotic genes, interactions between genes and hormones, and gene regulation through methylation patterns, are but a few of the novel phenomena now within the grasp of molecular genetics (Lewin, 1994). It seems to us that a comprehensive evolutionary theory should directly (not just implicitly) address the diverse effects of such phenomena.

(ii) Complexity and the inadequacy of linear models. Evidence of non-linearity of quantitative genetics parameters is increasingly common (e.g., Gifford & Barker, 1991 and references therein). The two major causes of such departures from linearity are the presence of genes with major non-additive effects and distribution asymmetry (see below). Impetus to expand to nonlinear modelling also comes from its successes in other fields of science: for example, in physics (Gulick, 1992) and in ecology (Hastings *et al.*, 1994) the acknowledgment of nonlinear effects has opened new horizons to theoretical research. The analytical intractability of nonlinear models is an objection that is less and less tenable given the rapid development of the so-called 'experimental mathematics' in the last thirty years (Mandelbrot, 1992). Because the methods of nonlinear dynamics use deterministic equations, in which each term has a direct physical or biological interpretation (even when using linear approximations: Altenberg, 1991), the argument that nonlinear terms do not have a biological meaning attached to them applies only to statistical approaches based on polynomial regression.

One of the reasons for the power of short term predictions in quantitative genetics is that linear models are very robust: even if the underlying dynamics are completely

nonlinear, linear approximations will still explain high percentages of variance in most cases (in particular, in any case in which the true function is monotonically increasing or decreasing). On the other hand, two cautionary notes should be remembered about favouring simplest models for the sake of their simplicity: (a) it is well known that even very small nonlinear effects can exponentially accumulate until they completely alter any long-term trajectory predicted by the model (the so-called 'butterfly effect': Lorenz, 1963). (b) Contrasting simple vs. complex models to fit data about ecological time series, Turchin and Taylor (1992) demonstrated that most of the interesting dynamics are completely obscured when one wields Occam's razor.

(iii) Ubiquity of gene-gene and gene-environment interactions. The evidence for pervasive epistatic effects of genes is by now overwhelming (Wright, 1980 and references therein). Extensive data from molecular genetics clearly point to the same conclusion. Genotype by Environment interactions, otherwise known as genetic variation for plasticity, are also a common feature of natural biological variation (reviews in Bradshaw, 1965; Schlichting, 1986; Sultan, 1987; West-Eberhard, 1989; Scheiner, 1993). Therefore, assumptions of additivity should be regarded with caution. The objection that interaction effects typically explain only low percentages of variance can be subjected to the same criticism just raised for the supposed minor role of nonlinear effects. The dictum that only additive genetic variation responds to selection carries a lot less weight once it is realized that nonlinear and interactive components of variance can also show substantial levels of 'additive' variability, when this is defined as anything that reacts to selection (cases of selective response of G by E interactions, for example, are very common: see Falconer, 1990 and Scheiner, 1993 for reviews). Also, several studies have now ascertained that, after exposure to novel environments or population bottlenecks, non-additive genetic variance can be 'transformed' to additive and therefore evolutionarily 'useful' variance (Bryant *et al.*, 1986; Goodnight, 1988; Tachida & Cockerham, 1989; Willis & Orr, 1993).

(iv) Alternatives to normality and multinormality. A few authors have started to explore the consequences of violating the assumption of normality in quantitative genetics. Turelli and Barton (1990), for example, compared the predictions of a Gaussian model with those of a multilocus population genetic model (a more realistic approximation to the description of many characters). Although the short-term predictions of the two models were very similar, the long term dynamics turned out to be completely different. Furthermore, they showed that even if the genetic variance is attributable to many loci with small effects (which yields the normality of the distribution), selection will alter the distribution of breeding values, creating strong deviations from the Gaussian approximation through multilocus linkage disequilibria.

(v) Evolution far from equilibrium. As was realized for the case of classical thermodynamics (Gregoire & Prigogine, 1989), it is just as improbable that biological systems will spend long stretches of time at or near any state that can be defined as 'equilibrium'. Our quest for equilibria is more likely a result of our thirst for simplicity and of our limited mathematical tools (Prigogine, 1980). Altenberg (1991) demonstrated that even the relatively simple (linear) equations for frequency-dependent selection at one locus can produce very complex dynamics, and that the system never settles to any equilibrium for a wide range of biologically reasonable values of the key parameters. Akin (1983) had

previously demonstrated that non-simple dynamics and non-equilibria can result from standard two locus population genetic models.

(vi) Evolution in changing landscapes. The assumption of the constancy of the fitness landscape, as we already pointed out, ignores any frequency-dependent selection. Arguments have been proposed (Wallace, 1989, 1991), that frequency dependent selection may be the ***most common selective regime*** under natural conditions. Empirical evidence and models of speciation and extinction rates show that the fitness landscape is bound to change constantly over evolutionary time (Van Valen, 1973; Stenseth & Maynard Smith, 1984). Lewontin (1978; Levins & Lewontin, 1985) has repeatedly advocated that evolution in changing landscapes is a necessary result of the dialectic nature of the evolutionary process. Quantitative genetics can accommodate alterations in the adaptive landscape only by resetting the model parameters based on empirical data, a meagre achievement for a purposefully general theory of evolution.

(vii) Evolution and the nature of G. Perhaps the most difficult assumption of quantitative genetics to justify in an evolutionary context is one of the most crucial: the constancy of the genetic variance-covariance matrix. It has been questioned on theoretical grounds by Schlichting (1986) and Turelli (1988), and experimentally by Wilkinson *et al.* (1990) and by Mazer & Schick (1991a,b), among others. It is known that simple changes in the environment can dramatically affect the magnitude and sign of genetic correlations (Mazer and Schick, 1991a,b; Campbell, 1996), and that a few generations of artificial selection have the same effect (Wilkinson *et al.*, 1990). These results are to be expected on the basis of the genetic theory of evolution itself: given that evolution is defined as a change in allele frequencies (Hartl & Clark, 1989), any major evolutionary phenomenon (selection, drift, migration, mutation) has the potential to change the variance-covariance structure of a population. A constancy of G is almost the opposite of evolution (at least in the long term).

Via and Lande (1987) argued that G is theoretically robust to relatively large perturbations, but such perturbations were on the time-span of one generation only, preceded and followed by stabilizing selection. The scenario is likely to be very different if we consider long-term changes in the external environment, or directional selective forces for sustained amounts of time. On the other hand, it is also clear that the genetic covariance between *some* traits will tend to remain constant even at macroevolutionary scales (in fact, some traits do not show any variation at all). Therefore, any discussion of the constancy of G should be put within the context of a particular empirical study. Another source of problems for the widespread use of G has been pointed out by Houle (1991). If the underlying genetic structure is hierarchical (i.e., if some genes affect the phenotypes indirectly, through their action on other genes or traits), then the observed genetic covariances are a complex function of gene effects and of the number of genes involved in the pathway. This is a clear example of the limitations implicit in models that do not address the mechanisms of the genetic control of phenotypes. More generally, Gromko (1995) has shown that a particular genetic correlation does not uniquely identify a set of pleiotropic relationships: he concluded that a population's ability to evolve may be strongly genetically constrained even in the absence of any measurable genetic covariance among traits; conversely, a strong genetic correlation may not reliably indicate any fundamental genetic constraint. This represents a major, yet so far unappreciated, blow to the rationale of using genetic variances and covariances to model long-term phenotypic evolution.

(viii) The nature of phenotypic plasticity: allelic sensitivity vs. gene regulation. We have argued elsewhere (Schlichting & Pigliucci, 1993, 1995) that phenotypic plasticity can be based on at least two distinct types of genetic control: allelic sensitivity and gene regulation. Under allelic sensitivity, the same genes influence the expression of the trait in different environments, but their reaction is different (much in the same way that a single enzyme has different reaction rates at different pH values). With gene regulation, one or more regulatory elements are the only (or the main) genes actually sensitive to the environment, and they switch on or off suites of genes responsible for the structural expression. We have shown that quantitative genetics does not deal effectively with regulatory mechanisms, and that a genetic correlation can confound the effects of different causes (Schlichting & Pigliucci, 1993, 1995). While genetic correlations are blind to the mechanistic basis of genetic control, it is precisely the type of mechanism involved in the expression of a phenotype that determines the qualitative response to selection, and therefore the evolutionary trajectory.

(ix) The nature of development: local gene action and 'emergent' epigenetic properties. The strategy used in quantitative genetics to deal with ontogeny and epigenesis is either (a) to consider each stage in ontogeny as a distinct character, genetically correlated to other stages of the same trait (Kirkpatrick & Lofsvold, 1992; Slatkin, 1987), or (b) to add more terms to the analysis of variance, each one representing additional sources of variance, such as 'epigenetic' or 'maternal' effects. It is then a matter of devising experimental designs that allow the independent estimation of such terms (Atchley & Hall, 1991). We believe that neither of these approaches effectively accounts for the kind of phenomenon that development actually is, or how 'emergent' epigenetic properties do emerge. Turing (1952), and more recently Nijhout *et al.* (1986), convincingly argued that epigenetic phenomena are the direct result of local gene action. The genotype does not act as a 'blueprint' for the organism, but as a set of rules that direct the action of genes in particular local (cellular) environments. The understanding of complex phenomena like the effects of heterochronic changes at the gene level, or the emergence of apparently heterochronic phenomena from changes in gene action that do not actually interfere with timing of action, are simply not within the realm of application of quantitative genetics, and require mechanistic computer simulations (Nijhout *et al.*, 1986; Emlen *et al.*, 1993; Pigliucci, Schlichting, Jones, & Schwenk, in press). Quantitative genetics, like any other scientific theory, has to have limited objectives if it is to be effective. Perhaps the emphasis in the last decade has been on trying to explain too much biology with too little mathematics.

6. WHAT ALTERNATIVES ARE AVAILABLE?

Having pointed out the assumptions of quantitative genetics, and the complexity of the type of system we wish to model, the logical question is: are there alternatives available, and if so, how should they be integrated with our current knowledge of genetics and evolutionary processes? In this section, we will briefly discuss the advantages and limitations of three alternative approaches to classical quantitative genetics modelling. It is clearly not within the scope of this paper to discuss in details the methodologies of each approach, or even less to work through examples of applications. Furthermore, *there might simply not be a viable alternative available right now or in principle,* forcing us to accept

what is becoming clear to physicists and meteorologists: an understanding of a class of natural phenomena *does not necessarily translate* into an ability to predict or control them.

(i) Nonlinear dynamics and chaos theory. Let us again consider our parallel between quantitative genetics and classical thermodynamics, both examples of 'first approximations' limited by the inadequacy of available mathematical tools. What happened in thermodynamics and other fields of physics might provide a model also for evolutionary genetics. In the last thirty years, linear approaches in physics have gradually been replaced, or at least expanded, by the use of nonlinear dynamics techniques (Gulick, 1992). Nonlinear modelling is made possible both by advances in computer technology (it relies mostly on computerized iterative procedures) and in mathematical theory (basins of attraction, attractor loci and Hopf bifurcations in place of simple fixed equilibria). Nonlinear dynamics is often regarded as synonymous with chaos theory, but chaotic attractors are only one special (although admittedly very interesting) category of nonlinear phenomena.

Applications of nonlinear dynamics theory to biology are by now common in physiology and ecology (May, 1976; Hastings *et al.* 1994), but have been rare in population genetics (Akin, 1983; Altenberg, 1991) and developmental biology (Emlen *et al.*, 1993). Yet, it has been demonstrated that: (a) simplified linear models can completely miss complex dynamics that are revealed by nonlinear techniques (Turchin & Taylor, 1992); and (b) that even very simple deterministic population genetics models can yield fairly complex nonlinear behaviours (Akin, 1983; Altenberg, 1991).

Nonlinear modelling overcomes several of the limitations of quantitative genetics: (1) it is a mechanistic, not a statistical approach; (2) it does not assume linearity (obviously); (3) it does not assume additivity (interactions are readily modelled); (4) it does not depend on multinormality of the variables included in the model; (5) it is a dynamic approach, not limited to the search for equilibria (although these can be described as special cases), or to the exploration of system behaviour around equilibrium regions; (6) it does not assume evolutionary constancy of any parameter, and even the functions describing the state of the system can be altered at any point in time through feedback loops. On the other hand, the following limitations apply: (1) a biologically interpretable set of differential equations has to be available (as in the case of frequency-dependent selection); (2) although potentially unlimited, the complexity of the system of equations is constrained by computer power; (3) it is often not possible to obtain general analytical solutions for a problem, forcing the investigator to intensively explore a limited subset of the parameter space; (4) even if the relationships among variables turn out to be highly ordered, single trajectories of the system in time might be unpredictable *in principle* (because of the butterfly effect, Lorenz, 1963).

(ii) Complexity theory and evolution in rugged adaptive landscapes. Complexity theory is an even newer branch of mathematics, that includes (or, better, is an extension of) nonlinear dynamics and the old catastrophe theory proposed during the seventies by Rene' Thom (Pines, 1986; Gregoire & Prigogine, 1989; Zeeman, 1973; Waddington, 1974; Saunders, 1980; Thom, 1983). Most of complexity theory makes use of computer simulations in a manner radically distinct from both quantitative genetics and nonlinear dynamics. Computers are here used as a tool intermediate between mathematical theory and experiments (Arthur, 1988). One of the basic applications of complexity theory is the study of the evolution of genetic algorithms (von Neumann, 1966; Holland, 1986; Kauffman & Smith, 1986): the system to be modelled is 'recreated' inside the computer, not by means of equations representing key variables, but by using algorithms that interact in a way

parallel to the system of interest (Ray, 1992). A biologically relevant example is the simulation of epigenetic emergent properties during the development and phylogeny of cellular automata presented by Nijhout *et al.* (1986) mentioned above. They were able to replicate many of the fundamental characteristics of living developmental systems and of their phylogenetic relationships by simulating the evolution of a cellular automaton whose 'development' was governed by local 'genetic' rules. Complexity theory has also provided new insights into the study of evolution in rugged adaptive landscapes (Kauffman & Levin, 1987) and the behaviour of complex systems in general (Wolfram, 1984; Langton, 1986; Bak *et al.*, 1988).

Kauffman (1991, 1993), in particular, has investigated the properties of genetic networks of increasing complexity (measured by the average number of interactions among elements). He concluded that additive systems with no regulation will tend toward a single, stable equilibrium (analogous to Fisher's fundamental theorem), but also that they would not be able to escape from local peaks characterized by sub-optimal conditions. At the opposite extreme, too much interconnection among regulatory elements would make the system prone to 'complexity catastrophes', ultimately prohibiting any evolutionary advance. Intermediate systems with localized epistatic interactions among genes, however, turned out to be evolutionarily extremely flexible and capable of interesting behaviours that have parallels in real genetic systems (the so-called 'evolution at the edge of chaos').

Most of the limitations inherent in the assumptions of quantitative genetics do not apply to complexity theory in principle. This is because of the very different meaning of the word 'modelling' in complexity theory, as explained above. On the cautionary side, it is not clear where exactly complexity theory can lead. The field is so young, and the tools so different and new, that so far it represents an almost unexplored set of possibilities. It is certainly not possible to use complexity theory for precise predictions about the evolution of specific systems. Complexity theory deals with the understanding of the relationships between patterns and processes, and with the description of general categories of behaviour, not with specific prediction about real systems (analogously to nonlinear dynamics). Whether this is a limitation of this science, or an inherent property of complex systems we simply have to live with, is a matter for philosophy of science and future research (Depew & Weber, 1995).

(iii) Game and optimization theory. The final alternative approach to be discussed here is probably the most familiar to many biologists, and it consists of applications of game theory (or more generally, optimization theory) to characterize evolutionarily stable strategies (ESS) (Maynard Smith, 1982). Game theory has been applied mostly to the determination of conditions favouring the evolution of particular behaviours (Futuyma, 1986; Moore & Boake, 1994), but it can be used to describe evolution of life-histories or of phenotypic plasticity (Stearns & Koella, 1986; Houston & McNamara, 1992). Basically, optimization theory sets up a system of equations describing advantages, disadvantages and trade-offs implicit in behaving one way or another (or in having one phenotype or another), or in adopting mixed strategies. The researcher then tries to determine the evolutionary outcome by analytical solution or by computer iteration.

The advantages of optimization theory over quantitative genetics reside in its deterministic approach, and in its independence from most of the assumptions already discussed. In this sense, the theory parallels several of the characteristics of nonlinear modelling, and it is mostly helpful in clarifying towards which end - under optimal

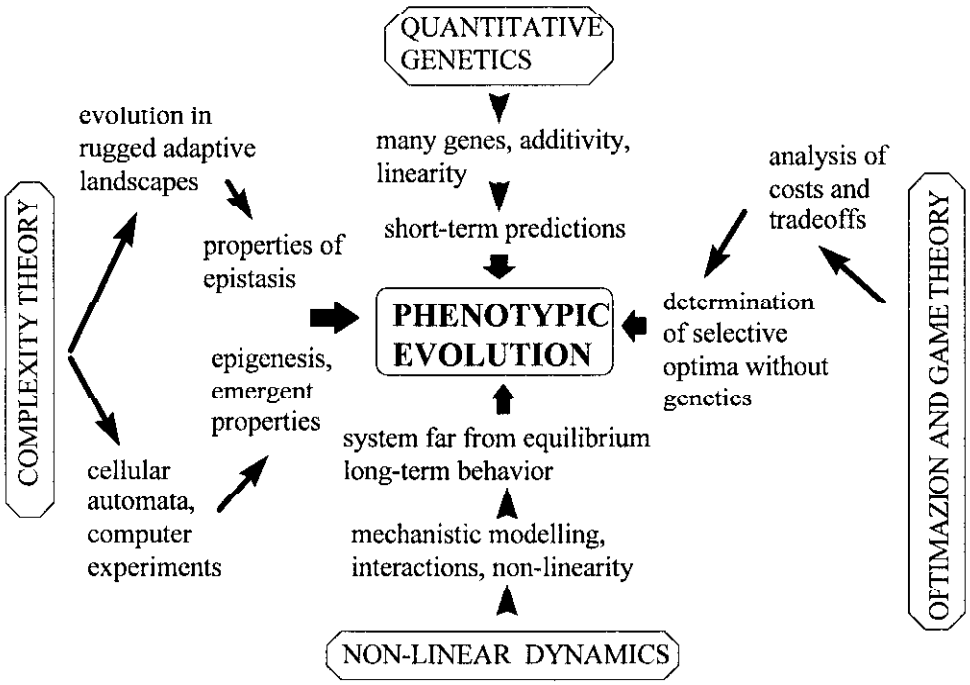

Fig. 1. 'Concept map' illustrating our perception of the relationships among several disciplines and approaches used to study phenotypic evolution. See text for details.

conditions - natural selection will push the system. Optimization modelling has, however, two major disadvantages: (1) there still is an implicit or explicit 'search for equilibria' (evident in the choice of the term Evolutionary *Stable* Strategy), although this is mostly in the applications published so far, not inherent in the mathematics. (2) There is no genetics: the theory implies that whatever parameter of the model has to evolve, it will do so because the appropriate genetic variability (of whatever nature) will be there. When optimization theory equations are interpreted in a genetic sense, they are simply equivalent to a quantitative genetic model of one locus with multiple alleles, and they are affected by the same limitations (Charlesworth, 1990; Abrams *et al.*, 1993).

7. TOWARDS A THEORETICAL SYNTHESIS?

Should we abandon quantitative genetics, and if so, which alternative should we embrace? The concept map in Fig. 1 summarizes the characteristics, advantages and relationships of the alternatives discussed in this paper, including quantitative genetics. As any concept map (Novak & Gowin, 1984), it only represents our peculiar vision of the subject matter, and connections could be rearranged, strengthened or eliminated according to different perceptions. However, the point is that the modelling of phenotypic evolution

and of its genetic basis is far from being a simple issue. Consequently, we do not envision the triumph of one procedure over another, but a proper integration of different approaches.

It is clear from the map, for example, that only quantitative genetics and nonlinear dynamics do actually include any genetics as we know it. Quantitative genetics is particularly appropriate (a) whenever its simplifying assumptions reasonably hold, and (b) if the goal is the prediction of short-term evolution (when G can be assumed to be nearly constant). *The major problem with quantitative genetics is probably that it has been expanded to investigate areas and answer questions that it was not designed to address.* This is the main reason why we need a new theoretical synthesis, possibly including still other approaches not pictured in our concept map. Nonlinear dynamics deals with long-term evolution, but is probably intrinsically incapable of yielding precise predictions on specific cases. On the other hand, it trades this handicap with the potentiality of an understanding of the mechanistic basis of evolutionary dynamics and the patterns that they generate. Complexity theory, with its emphasis on computer experiments and algorithmic modelling, clearly interfaces with both quantitative genetics and nonlinear dynamics. Its promise is to lead to an understanding of the evolutionary characteristics of systems of different levels of complexity. Also, it shows us what type of phenomena can be associated with the terms 'epigenesis' and 'emergent properties', and how they can be accurately reproduced mechanistically. The objective of game and optimization theory is to describe a Panglossian world without genetic constraints. It answers questions of the type: what is the outcome of evolution, given certain starting conditions and unlimited genetic variability? Its interaction with the genetically based approaches should provide an understanding of the balance between selective agents and genetic limitations, which result in the origin of actual phenotypes.

According to Lewontin (1991), there are two fundamental categories of biologists: the Platonists and the Heracliteans. The Platonists think that the world is basically at equilibrium, and any deviation from it is only temporary. The Heracliteans, on the other hand, thrive in permanent uncertainty and never-settling dynamics. A synthesis on some intermediate ground seems at this point essential.

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