Book Reviews

The Genetical Theory of Natural Selection. A Complete Variorum Edition. By R. A. Fisher (edited with foreword and notes by J. H. Bennett). Oxford University Press. 1999. ISBN 0-19-850440-3. xxi + 318 pages. Price £25.00.

The Genetical Theory of Natural Selection is surely the most important book on evolution after *The Origin of Species*. Seventy years after its publication, its originality and fertility of ideas never cease to astonish, and many of Fisher's contributions still influence contemporary research. The publication of this variorum edition is greatly to be welcomed. The main body of the text is that of the original 1930 edition; the amendments made in the 1958 Dover edition are placed in an appendix. There is also an introduction by Henry Bennett, with comments on the historical context and main implications of Fisher's work in evolutionary genetics, as well as another pair of appendices with extracts from some of his letters, and a list of his publications on population genetics.

Fisher's achievement, rivalled of course by Haldane and Wright, was to integrate transmission genetics and evolutionary theory. This led to the revival of population-level, Darwinian, thinking on evolution after a long period of neglect and misunderstanding by the majority of biologists. In the first chapter, Fisher showed that, far from there being a conflict between Mendelism and Darwinism as supposed by many of the early geneticists, the preservation of variability under particulate inheritance is crucial for the operation of natural selection. If Darwin had arrived at a Mendelian view of inheritance, he would not have been so ready to accept a role for the inheritance of acquired characteristics. Fisher further argued that the facts of genetics suggest that mutation has little role in directing evolution, leaving natural selection as the major guiding force of evolution. Few would today question these conclusions. In some sentences added to the 1958 Dover edition, he explicitly rejected the possibility of random genetic drift as having any broad evolutionary importance, on the grounds that the small populations required for drift to operate rapidly are likely to either become extinct, or to be swamped by the rest of the species (p. 273 of the new edition). In the light of the modern emphasis on the probable role of random fixation of neutral or nearly neutral mutations in molecular evolution, this conclusion now seems too sweeping. Nonetheless, the evidence accumulated since 1930 for the action of selection on phenotypic variability suggests that it applies to evolution at the level of morphology, behaviour etc.

In his second chapter, Fisher developed the mathematical theory of natural selection in terms of his famous 'Fundamental Theorem of Natural Selection', relating the rate of increase of mean fitness to the (additive) genetic variance in fitness. The argument, even with the more explicit derivation provided in the 1958 edition (pp. 274–78 here), is hard to follow. Exactly how Fisher intended the theorem to be interpreted is still a matter for debate, although subsequent work, especially by Kimura, has greatly clarified the conditions under which it holds as a good approximation. Fisher also developed his influential geometric model of the process of adaptation in a multi-dimensional character space, arguing that small random changes in such a space are more likely to confer increased fitness than large changes. This model has recently again become the focus of attention for theoretical studies intended to illuminate the interpretation of data on the genetics of adaptation.

Largely as a result of this work, Fisher is frequently portrayed in the contemporary literature as believing in a strictly additive basis for the inheritance of quantitative characters, and as dismissing any evolutionary importance for epistatic interactions in fitness effects. This is accompanied by a sub-text that this is in some way less virtuous than embracing a less 'reductionist' view, which assigns a prominent role to epistasis, as in Wright's 'shifting-balance' theory. This is, in fact, a travesty of Fisher's views. In the first place, the point of the Fundamental Theorem is not that non-additive variance in fitness does not exist, but that it does not directly determine the rate of progress under selection within a population. In the 1958 edition, Fisher explicitly pointed out that non-additive effects, such as those associated with inbreeding depression, may create selection pressures for traits such as inbreeding avoidance, without

violating the conditions of the Fundamental Theorem (pp. 278–79 here). Second, his whole theory of the evolution of dominance, the subject of the third chapter, relied on the concept of modifier genes that interact epistatically with the effects of the genes they modify. The importance of epistatic modifiers was also stressed in chapters six and seven that deal with speculation and mimicry, respectively. In chapter five, he proposed the possible existence of interactions between the fitness effects of alleles at polymorphic loci, and pointed out that this would lead to selection for reduced recombination frequencies. In one of the additions to the 1958 edition, he stated that '…the effects by which any gene-substitution is recognized depends on the results of interactions with, possibly, all other ingredients of the germ plasm…' (p. 280 here). This is hardly the position of a fervent advocate of additivity.

It is clear, therefore, that Fisher rejected the shifting balance theory, not because it invoked epistasis, but because of its appeal to genetic drift in small local populations. He also explicitly rejected supra-individual selection, in another addition to the 1958 edition (pp. 279–80 here). This was at a time when population level advantages to features of the breeding system such as recombination rates and inbreeding rates were the stock-in-trade of many prominent biologists, especially Darlington, Mather and Stebbins. It is interesting to speculate whether this denial of the efficacy of anything other than individual or kin selection (the latter is discussed in at least two places in the 1930 edition) was stimulated by their writings. It was not until the 1960's and 70's that Fisher's views on these issues had much influence outside the small body of population and ecological geneticists. Until the advocacy of the preeminent roles of individual and kin selection in the interpretation of behavioural evolution by figures such as Hamilton, Maynard Smith and Williams, most biologists appear to have been perfectly comfortable with evolutionary interpretations based on group selection.

The most formidable section of the book is Chapter 4, based closely on two papers published in 1922 and 1930 in the *Proceedings of the Royal Society of Edinburgh*. Fisher's methods and results laid the foundations for all subsequent work in the stochastic theory of population genetics, introducing the two basic techniques of branching processes and diffusion equations. Much subsequent work by Wright and Kimura flowed directly from this framework. In the hands of Kimura and Ohta, it provided the theoretical basis for the interpretation of molecular variation and evolution in the light of the neutral theory, somewhat ironically in view of Fisher's dismissal of the importance of drift.

If Fisher had done nothing else, this work would have placed him at the forefront of theoretical biologists. His results on the distribution of the 'numbers of segregating factors' under the balance between mutation and random extinction are equivalent to those for Kimura's infinite sites model of DNA sequence variation, now widely employed in studies of molecular variation. In this context, Fisher recognized the relation between population size and level of variability maintained at statistical equilibrium. The biological relevance of his findings could not be fully appreciated until the modern era of molecular population genetics. Furthermore his diffusion equation formula for the probability of fixation of a gene in a finite population is the basis for the fundamentally important conclusion that selection will dominate drift if the product of the population size and selection coefficient much exceeds one, which Fisher held to be the most likely situation in nature.

There are numerous other topics which Fisher either originated in *The Genetical Theory*, or on which he shed new light, including the theory of the evolution of the sex ratio, the evolution of female mating preferences, speciation with only partial geographic isolation, the maintenance of polymorphism by heterozygote advantage or by frequency-dependent selection, the maintenance of variation in quantitative traits under mutation and selection, and the theory of mimicry. While one of Fisher's most cherished ideas, the theory that the dominance of wild-type over deleterious mutant alleles has evolved as a result of the modification of the phenotype of heterozygotes in the direction of wild-type, has failed to survive empirical tests, the relevance of large portions of his work to modern evolutionary biology is astonishing.

The part of the book which seems most dated relates to human social evolution, where Fisher devoted much space to arguing that the higher fertility of the less able members of society was a major factor in the decay of civilization, by creating a selection pressure in favour of greater stupidity. This section seems generally to be ignored, or regarded as an embarrassment, by modern evolutionary biologists, and is frankly tedious to read. (But it is no worse than the rampant speculation that is current in evolutionary psychology.) As Henry Bennett notes in his introduction, Fisher made no amendments to this part of the book in the 1958 edition, and published little else on the subject. But, all in all, *The Genetical Theory of Natural Selection* is a scientific masterpiece, which deserves to be read by all serious students of evolutionary biology. It is wonderful to have this new edition available, at a reasonable price.

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Bioinformatics Methods and Protocols. Edited by S. Misener and S. A. Krawetz, Humana Press, 1999, ISBN: 0-896-03732-0, hardcover 500 + xii pages, $89.50.

The term 'bioinformatics' is sometimes applied to a wide range of activities that have nothing in common apart from the use of computers and a relationship to some aspect of biology. In contrast this book is focussed very narrowly on computer analysis of DNA and protein sequences, with a short section on electronic library services, and a few articles on miscellaneous other topics such as use of the polymerase chain reaction for carrying out computations (highly inefficient) or the possibility of escaping the tyranny of Windows software by switching to Unix (a more practical possibility).

The are two broad classes of article, which differ greatly in their value. The general level of the text is instruction on how to run particular programs. The most useful articles are in the second and third sections of the book (together somewhat under half the total length), and consist mainly of practical hints and guidance on using some well-known programs, packages and websites. There are equally useful Chapters on creating a local sequence analysis service using free Unix software and on home-building an image system for electrophoresis gels, and another with a long listing of free sequence analysis software for Windows and Macintosh PC's.

The less-valuable Chapters are superficially rather similar, but actually contain only a general outline of the facilities at websites or within particular packages. Oxford Molecular is strongly represented amongst the commercial companies whose products are presented in this way, but there are also contributions about packages from DNASTAR and BioTools Inc. In most cases these articles are not written by company employees, but in the absence of any critical comparison or evaluation, they give the reader nothing which could not be obtained as easily from sales literature or company websites.

What should the Editors have included in place of this material? Experimentalists are now rapidly expanding the boundaries of their use of bioinformatics beyond mere sequence analysis. Much molecular biology research is centred on organisms whose genomes have been completely sequenced. Database and interfaces encourage the researcher to take an integrated genome-perspective view of genetic, biochemical and structural information in addition to sequence. High-throughput methods, such as nucleic acid chips for studying gene expression, have the potential to deliver large volumes of data whose analysis will require clever software in addition to clever biologists. These developments are scarcely referred to in this volume.

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Population Genetics of Multiple Loci. By F. B. Christiansen. Wiley Series in Mathematical and Computational Biology, ed. S. Levin. John Wiley & Sons. 1999. ISBN 0 471 979791. 365 pages. Price £80 hardback.

Much of evolution consists of 'bean bag genetics' (Haldane, 1964), in which genes are taken to be randomly combined in the population. An allele increases in frequency if, on average, it increases fitness; this average is taken over all the environments and all the genetic backgrounds in which the gene finds itself. However, departures from random combination ('linkage disequilibria') are crucial to many evolutionary phenomena. Selection can be detected through its influence on linked markers, and is limited by interference between selected loci (Hill & Robertson, 1966). The variance of quantitative traits, on which the response to selection depends, is shaped by linkage disequilibria (Bulmer, 1971). The flow of genes between diverging populations is impeded by the strong associations generated by admixture (Barton, 1979). Genes that modify features of the genetic system such as recombination and mate preference are selected indirectly, through their associations with selected genes (Feldman *et al*., 1996). Thus, while much of adaptation and speciation can be understood using simple single-locus population genetics, important phenomena involve the joint evolution of multiple genetic loci.

The *Population Genetics of Multiple Loci* does not attempt a broad treatment of all these issues. Rather, it is a review of work by the Stanford school of theoretical population genetics, and an exposition of a multilocus notation developed by Christiansen. Much of our modern understanding of how systems of multiple loci evolve is due to work by Karlin, Feldman and their collaborators (e.g. Karlin & Feldman, 1970; Karlin, 1975). The initial motivation was to explain the high levels of genetic variability revealed by electrophoresis; interest therefore concentrated on equilibria under balancing selection. Even the simplest model of two loci, each with two alleles, is difficult to analyse, and so symmetrical models were studied. However, it has proved difficult to generalise from these results to more loci and to more general fitness schemes. Because simple models can behave in surprising ways, it is dangerous to extrapolate from special cases to the complex and unknown interactions among large numbers of genes in natural populations. For example, there can be stable states in which at

each locus, the heterozygote is *less* fit than the homozygotes (Hastings, 1982), and there can be stable limit cycles even when fitnesses are fixed (Hastings, 1981).

There has been a substantial advance in recent years in our understanding of the dynamics of multilocus systems. Partly, this has resulted from advances in computer technology, increasing our power to simulate and numerically analyse evolving systems. Even the fastest computer cannot, however, simulate deterministic evolution of more than a dozen or so loci, and so most of the advances have relied on mathematical analyses. Yet the real breakthroughs in our understanding of evolutionary dynamics have not been with exact multi-locus models but rather with the development of more approximate and general models. In many cases, reasonable approximations (for example, allowing weak selection or very many genes) have made unsolvable problems tractable. Such methods have made major contributions to our understanding in such diverse areas as the maintenance of variation in continuous traits (Lynch & Walsh, 1998), the evolution of genetic systems (Feldman *et al.*, 1996), and the evolution of DNA sequences (Hudson, 1990).

Christiansen develops the population genetics of multiple loci using a straightforward notation. At each locus, two alleles segregate (labelled '0' and '1', say). The frequency of the haploid genotype carrying '1' alleles at the set A of loci is written $\pi(\mathrm{A})$, and the frequency of the diploid genotype carrying '1' alleles at the set A of loci from the mother, and the set B from the father, is written $\pi(A, B)$. Recombination is described by $R(K)$, which is the proportion of gametes that derive the set of loci K from the paternal genome, and the remaining loci from the maternal genome. This formalism is used to set out some general results in a unified framework: for example, on the influence of recombination on the increase of rare genotypes (the schemata theorem; Holland, 1975); the strength of linkage disequilibria under weak epistasis (quasi-linkage equilibrium; Kimura, 1965); and the strength of selection against recombination under constant selection (the reduction principle; Feldman *et al.*, 1996). The expression (7.19) for the linkage disequilibrium $\hat{D}_M$ among a set of loci M at quasi-linkage gives an idea of the notation:

$$\hat{D}_M \approx \frac{\epsilon \hat{\pi}^R_M(\phi)\,\hat{\pi}^R_M(M)\,\hat{C}_M}{1-2R_M(\phi)} \qquad (1)$$

Here, ϵ is a small quantity proportional to the strength of selection; $\hat{C}_M$ is a measure of epistasis amongst the set M; $\hat{\pi}^R_M(\phi)\,\hat{\pi}^R_M(M)$ is the frequency of M gametes at linkage equilibrium (which is just a product of allele frequencies); and $R_M(\phi)$ is the chance that at meiosis, a gamete derives all the genes in the set M from the maternal genome. This example shows that relatively simple results can be derived for arbitrarily many loci. However, Eq. 1 hides some of the complications, because the coefficient of epistasis involves a sum over the fitnesses of all genotypes, with weights that depend on recombination rates. In most instances, such compact formulae cannot be obtained; thus, Christiansen's discussions of the biological implications of multilocus theory do not for the most part flow directly from this formalism.

Christiansen (1987) began developing his notation in order to analyse the effects of migration between populations. I used a similar notation at about the same time (Barton, 1986), and with the same aims; this coincidence may be because migration yields to a particularly simple analysis, which can readily be applied to observations on hybrid populations. The results are quite similar: for example, Eq. 1 is equivalent to Barton and Turelli's (1991) Eq. 25. Christiansen's exposition is restricted to two alleles; however, it can be extended to any number of alleles by using repeated indices to represent higher moments (Barton & Turelli, 1991). (Contrary to Christiansen's statement on p. 178, this does not imply any restriction to additive traits or weak selection). Another difference between these approaches is in the treatment of selection. In Christiansen's treatment, coefficients of epistasis are either defined for particular models, or emerge from the analysis (e.g. $\hat{C}_M$ above). Rather more general results can be found by describing selection either as a polynomial function of genotype, or selection gradients (Barton and Turelli, 1991).

It would be helpful to see how Christiansen's methods relate to other approaches. For example, the coefficients of linkage disequilibrium $\hat{D}_M$ defined by Christiansen are equivalent to the coefficients defined by Slatkin (1972), and to the central moments of Barton and Turelli (1991); Christiansen's linear measures of disequilibrium are equivalent to non-central moments. This equivalence is not immediately obvious. Similarly, it would be useful to see explicitly the relation between Christiansen's measures and the cytonuclear associations defined by Asmussen and Arnold (1991); the cumulants introduced by Burger (1991) and Turelli and Barton (1994); and Bennett's (1954) principal components. Although the diversity of measures of multilocus association can be baffling, it is no bad thing: different measures are appropriate for different purposes.

This book makes an excellent contribution by bringing together in one volume most of the results from the last three decades' work by the Stanford school, and by presenting it in a uniform notation. The algebra is straight-forward (if daunting at first), and is leavened by frequent illustrations from a few well-chosen biological systems. The index and glossary are well laid out, making this a valuable reference work. It is remarkable that the combination of

Mendelian genetics with Darwinian natural selection leads to an elegant theoretical structure, which raises challenging problems that are of both mathematical and biological interest. However, it remains to be seen whether the formal analysis of this structure, set out so clearly in this book, will lead to a general understanding of how populations in fact evolve.

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