

Fisher's Fundamental Theorem of Natural Selection

Steven A. Frank and Montgomery Slatkin

Fisher's Fundamental Theorem of natural selection is one of the most widely cited theories in evolutionary biology. Yet it has been argued that the standard interpretation of the theorem is very different from what Fisher meant to say. What Fisher really meant can be illustrated by looking in a new way at a recent model for the evolution of clutch size. Why Fisher was misunderstood depends, in part, on the contrasting views of evolution promoted by Fisher and Wright.

R.A. Fisher and Sewall Wright, two of the founders of modern evolutionary theory, fought bitterly for 30 years. Angry words were exchanged on a variety of topics, but at the heart of the controversy was a clash between each scientist's vision of natural selection and evolution: on one side, Fisher's Fundamental Theorem of natural selection, and on the other side, Wright's Adaptive Landscape.

Fisher detested the Adaptive Landscape formulation of natural selection, an opinion that he repeated on many occasions. Although Wright's original formulation¹ of the Adaptive Landscape in 1932 is obscure², the Adaptive Landscape soon came to mean that gene frequencies change as if proceeding up a hill of increasing average fitness. Wright justified this metaphor by showing that under some conditions the rate of change in gene frequency depends on the steepness of the gradient in average fitness, $d\bar{W}/dq$, where \bar{W} is the average fitness of the population and q is gene frequency.

Fisher objected to the idea that natural selection alone would have any simple effect on the average fitness of the population. For example: 'In regard to selection theory, objection should be taken to Wright's equation [the expression $d\bar{W}/dq$] principally because it represents natural selection, which in reality acts upon individuals, as

though it were governed by the average condition of the species or inter-breeding group' (Ref. 3, p. 58).

Fisher also pointed out that average fitness, measured by the intrinsic (malthusian) rate of increase of a species, must fluctuate about zero (Ref. 4, pp. 41–45). Otherwise, if a species' rate of increase were consistently positive, it would soon overrun the world, or if a species' rate of increase were consistently negative, it would quickly become extinct.

These comments about average fitness, repeated in different ways by Fisher, seem to contradict his own proud claims for his Fundamental Theorem of natural selection: 'The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time' (Ref. 4, p. 37), or 'The rate of increase of fitness of any species is equal to its genetic variance in fitness' (Ref. 4, p. 50). If 'fitness of any species' is interpreted as 'average fitness', which is the usual interpretation, these statements certainly suggest that the average fitness of a species increases steadily over time, just as in Wright's Adaptive Landscape.

Everyone, including Wright, interpreted Fisher as saying that the Fundamental Theorem was about the average fitness of a species. In fact, Wright often quoted the Fundamental Theorem in support of his gradient formulation of the Adaptive Landscape, $d\bar{W}/dq$. As pointed out by Ewens⁵, Wright said in his last paper: 'The effects [on gene frequencies in an Adaptive Landscape] may be calculated using Fisher's fundamental theorem of natural selection' (Ref. 6, p. 118), in spite of the fact that Fisher had already rejected this interpretation: 'I have never, indeed, written about $\bar{w}|\bar{W}$ and its relationships . . . the existence of such a potential function [i.e. a function nondecreasing in time] . . . \bar{w} is not a general property of natural populations, but arises only in the special and restricted cases Wright . . . considers' (Ref. 7, p. 285).

Here, we reconsider Fisher's Fundamental Theorem and its

relationship to Adaptive Landscapes. We focus on three questions: What did Fisher really mean by the Fundamental Theorem? Is Fisher's interpretation of the Fundamental Theorem useful? Why was Fisher misinterpreted, even though he stated on many occasions that he was not talking about the average fitness of a population?

What did Fisher really mean?

The standard interpretation of the Fundamental Theorem is that natural selection increases the average fitness of a population at a rate equal to the genetic variance in fitness. Thus, the average fitness of a population is a nondecreasing quantity. This interpretation is in accord with the intuitively appealing idea that natural selection will make species better adapted to their environments.

One problem with the standard interpretation of the Fundamental Theorem is that, although Fisher claimed that his theorem is exact, realistic models show that average fitness does not always increase. For example, Moran⁸ showed that average fitness can decrease when selection acts on two linked loci that have epistatic effects on fitness (see Box 1 for definition of genetical terms). In general, the average fitness of a population increases at a rate equal to the additive variance in fitness only when certain restrictive conditions are met. For example, there must be no epistasis, no linkage disequilibrium and no frequency dependence, among a variety of other conditions about mating and nonadditive genetic interactions^{10,11}.

Given that the standard interpretation was generally believed to be what the Fundamental Theorem was about, several theoreticians beginning with Kimura¹² have focused on the question of when the average fitness of a population increases at a rate approximately equal to the additive variance in fitness. Recently, Nagylaki¹³ has obtained upper bounds on the error made in assuming that the average fitness increases at a rate equal to the additive variance in fitness.

However, Price¹⁴ and Ewens⁵ have shown convincingly that the standard interpretation is very different from what Fisher had in mind,

Steven Frank is at the Dept of Ecology and Evolutionary Biology, University of California, Irvine, CA 92717, USA; Montgomery Slatkin is at the Dept of Integrative Biology, University of California, Berkeley, CA 94720, USA.

and they propose an alternative explanation that fits all the facts. Price and Ewens provide formal derivations of the Fundamental Theorem consistent with Fisher's interpretation: the theorem is exact and general in every way that Fisher claimed. Our purpose here is to provide a sense of what Fisher meant rather than to repeat the mathematical and historical analyses provided by Price and Ewens.

Fisher realized that the average fitness of a group is a useful quantity only in the wider context of other groups and the environment: a species in the context of competitors, diseases and food availability; a genotype in the context of a particular mix of competing genotypes within the population; or an allele in the context of the frequency of competing alleles at a locus.

To explain the notion of factors extrinsic to the group being analysed, Fisher referred to all extrinsic forces as the environment. The total change in fitness over time, in the context of the environment, E , can be defined as

$$\Delta \bar{W} = \bar{W}' | E' - \bar{W} | E$$

where primes denote one time step or instant into the future, and $\Delta \bar{W}$ is the total change in fitness which everyone had assumed was the object of Fisher's analysis.

Fisher's theorem, however, was not concerned with the total evolutionary change, which depends at least as much on changes in the environment as it does on natural selection. Instead, Fisher partitioned the total change into

$$\Delta \bar{W} = (\bar{W}' | E - \bar{W} | E) + (\bar{W}' | E' - \bar{W}' | E) \quad (1)$$

Fisher called the first term the change in fitness caused by natural selection because there is a constant frame of reference, the initial environmental state E . The Fundamental Theorem states that the change in fitness caused by natural selection is equal to the additive variance in fitness. Fisher referred to the second term as the change caused by the environment, or more often, as the change caused by the deterioration of the environment, to

stress that this term is often negative because natural selection increases fitness but the total change in fitness is usually close to zero.

Is Fisher's interpretation useful?

Price¹⁴ and Ewens⁵ both expressed deep disappointment in the Fundamental Theorem, and Nagylaki¹³ has recently echoed that disappointment. Price states (Ref. 14, p. 139): 'A ... [grave] defect is the matter of the shifting standard of 'fitness' that gives the paradox of $M[\bar{W}]$ tending always to increase and yet staying generally close to zero. Much more interesting would be a theorem telling of increase in 'fitness' defined in terms of some fixed standard.'

It is a matter of taste whether a particular partition of evolutionary change is useful; all of the component parts must ultimately sum to the same total change. We believe that Fisher's partition is useful – indeed fundamental. To support this conclusion, we analyse an interesting biological problem, the evolution of clutch size, and show that Fisher's view leads to a significantly deeper understanding of the problem. In discussing clutch size it is not our intention to resolve differences among various models, but instead to illustrate an application of Fisher's theorem.

The problem, presented in a recent paper by Cooke *et al.*¹⁵, is that many bird populations have considerable amounts of additive genetic variance for clutch size, and field studies typically show that larger clutch sizes would confer higher fitness. The paradox is often stated in terms of the standard interpretation of the Fundamental Theorem: average clutch size is expected to increase because there is significant additive genetic variance in fitness attributable to differences in clutch size, but clutch sizes in natural populations are apparently not changing.

Cooke *et al.* suggest that the average clutch size may remain fixed because of the balance between two forces: natural selection acts to increase clutch size, but a simultaneous increase in competition for scarce resources reduces clutch size. These authors stated that their model is an extension of the Fundamental Theorem rather than an

Box 1. Glossary

The following definitions provide a sense of how these concepts are typically used. Formal definitions for many of the following terms can be found in Falconer⁹ or in other introductory texts of genetics.

Average effect of a gene substitution can be illustrated by considering a locus that has two alleles, A and a . Let one randomly chosen a in the population be changed to A , and measure the phenotypic difference caused by the change. The average change, measured over all a 's taken one at a time, is the average effect of a substitution by a . The average effect of a substitution at this locus is the difference between the average effect of a substitution by a and a substitution by A . The average effect is the foundation for the concepts and mathematics of the Fundamental Theorem, and is also the basis for many of Fisher's criticisms of Wright.

Environment is an important aspect of the Fundamental Theorem. The average effect of an allele takes into account all possible genetic and environmental effects by measuring the phenotypic change of a substitution in the context of the current population. When discussing his Fundamental Theorem, Fisher chose to lump genetic effects such as gene frequency and dominance with physical effects such as weather into a single 'environmental' term.

Additive genetic variance is a measure for the potential amount of evolutionary change caused by natural selection. For a single locus, the measure is obtained by multiplying the square of the average effect of a substitution by the variance in gene frequency – essentially, the amount of change caused by a rise or fall in gene frequency multiplied by the amount of variability in genetic material presently available.

Epistasis is the genetic interaction between different loci. Epistatic interactions are non-zero if the average effect of a substitution at one locus depends on the genotype frequencies at a second locus.

Linkage disequilibrium is the statistical correlation between alleles at different loci. Linkage disequilibrium is nonzero if multi-locus gamete frequencies are different from the product of the allele frequencies at each locus.

Frequency dependence occurs when the absolute fitness (number of successful offspring) of a genotype depends on the frequency of genotypes in the population. **Density dependence** occurs when the absolute fitness of a genotype depends on the number of individuals in the population.

application of the theorem. They cite the standard interpretation of the theorem, including Wright¹⁶ and Crow and Kimura¹⁷, to support their conclusion.

In fact, Cooke *et al.*'s model is not an extension but a specific example of Fisher's partition of evolutionary change into a component caused by natural selection and a component caused by the environment. Fisher often referred to the environmental component as a 'deterioration in the environment', and, as one example, he discussed this deterioration in

terms of an increase in ecological pressure on population growth. We recast Cooke *et al.*'s argument in terms of Fisher's analysis in order to show the relationship between the clutch-size example and Fisher's ecological view of evolutionary change.

Cooke *et al.* consider clutch size, P , which can be equated to fitness. (P is used to denote phenotype.) P depends on two factors, $P = P_1 T_2$, where P_1 is the number of eggs per unit area of territory held by the bird, and T_2 is territory size. Territory, in turn, depends on

$$T_2 = (A/N)P_2/\bar{P}_2$$

where A is the total area available for territories, N is population size, and P_2 summarizes the physical and behavioral traits that determine aggressiveness and thus relative territory size. (All capital letters are random variables; overbars denote population averages.)

With these definitions, the clutch size, P , and the environmental influence on clutch size, E , are given by

$$P = P_1 P_2 E$$

$$E = A/N\bar{P}_2$$

From Eqn 1 above, the total change in the population mean for P is

$$\Delta\bar{P} = (\bar{P}'|E - \bar{P}|E) + (\bar{P}'|E' - \bar{P}|E') \quad (2)$$

The first term is the expected response to selection when measured in the context of the original environmental state; this response is equal to the additive variance in fitness. The second term is the contribution of changing environment to the total change in clutch size. This equation for the total change, $\Delta\bar{P}$, corresponds to the traditional quantitative genetic formulation (see Eqn 2 in Ref. 15).

The puzzle to solve is: why doesn't clutch size increase even though the first term, the additive variance in fitness for clutch size, is often quite large? Cooke *et al.* suggest that a decrease in the environmental term can strike a balance so that no evolutionary change in clutch size occurs.

In Cooke *et al.*'s model, there are two ways in which environmental

deterioration may occur. First, suppose that P_1 is fixed and that only the level of aggressiveness, P_2 , is variable. Then, from Eqn 2, the change in \bar{P} is zero because

$$\Delta\bar{P} \propto (\bar{P}'_2/\bar{P}_2 - \bar{P}_2/\bar{P}_2) + (\bar{P}'_2/\bar{P}'_2 - \bar{P}_2/\bar{P}_2) \quad (3)$$

where the first term is proportional to the increase in the average level of aggressiveness in the population caused by natural selection, and the second term is proportional to the decrease in clutch size caused by the increase in the average level of competition for space.

The second type of environmental deterioration occurs when P_2 is fixed and the number of eggs per unit area, P_1 , varies. In this case, the proportional change in P is given by

$$\Delta\bar{P} \propto (\bar{P}'_1/N - \bar{P}_1/N) + (\bar{P}'_1/N' - \bar{P}_1/N)$$

If one makes the reasonable assumption that the carrying capacity, N , is proportional to the number of eggs that can be raised per unit of territory, P_1 , then $\Delta\bar{P} = 0$. This balance occurs because the increase in efficiency caused by natural selection (the first term) is exactly balanced by the increased competition for space (the second term).

In this last case, clutch size and the intrinsic rate of increase (mean fitness) of the population do not change, but the population size does increase (see Ref. 18, p. 201). This is exactly the situation that Fisher had in mind for the only case in which he explicitly discussed the evolution of the total change in population mean fitness (Ref. 4, pp. 45-46):

An increase in numbers of any organism will impair its environment in a manner analogous to, and more surely than, an increase in the numbers or efficiency of its competitors. It is a patent oversimplification to assert that the environment determines the numbers of each sort of organism which it will support. The numbers must indeed be determined by the elastic quality of the resistance offered to increase in numbers, so that life is made somewhat harder to each individual when the population is larger, and easier when the population is smaller. The balance left over

when the rate of increase in the mean value of m [\bar{W}] produced by Natural Selection, is deducted the rate of decrease due to deterioration in environment, results not in an increase in the average value of m , for this average value cannot greatly exceed zero, but principally in a steady increase in population.

Another interesting aspect of Fisher's view is that gene-frequency change and evolution may be occurring continually even though there is no net change in mean fitness: 'Intense selective activity is shown to be compatible with an entire absence of change in the average survival value of the population' (Ref. 3, p. 63).

Why was Fisher misunderstood?

We think that Fisher was misunderstood because most evolutionary biologists sought a simple dynamic theory of evolution. That is what Wright's Adaptive Landscape provided. By contrast, Fisher did not seek a dynamic theory and, in fact, he believed that changes in fitness caused by natural selection could never be equated with the total evolutionary change in fitness. The first sentence in the preface of his book⁴, *The Genetical Theory of Natural Selection*, is: 'Natural Selection is not Evolution.'

When Fisher discussed the evolution of a trait, he generally considered the direct effect of natural selection, and the feedback caused by ecological changes due to natural selection. Instead of providing a precise description for the total change expected, he discussed at some length the difficulties involved in estimating all of the relevant selective and ecological parameters involved (Ref. 4, pp. 45-49).

Fisher's ecological, holistic view, and the very reasonable interpretation of clutch size that follows from this view, apparently leaves Fisher in a safe and comfortable position. But our discussion so far has not addressed two important issues. The first concerns Fisher's use of changing gene frequencies as an ecological factor subsumed within the environmental component of evolutionary change¹¹. The second issue concerns Fisher's criticisms of the Adaptive Landscape.

Fisher's peculiar treatment of changing gene frequency as part of the environment can be seen by an analogy with the clutch-size example of the previous section. In that example, the level of aggressiveness, P_2 , may evolve by the direct action of natural selection, as shown in the first term of Eqn 3, but the increase in the average value of aggressiveness, \bar{P}_2 , is treated as an environmental variable, in the second term of Eqn 3.

Fisher followed an analogous partition at the gene-frequency level. By his view, natural selection increases the frequency of a particular allele according to its average effect on fitness, which depends on the frequencies and combinations of other alleles – the genotypic 'environment'. Here allele frequency is a character correlated with fitness, and natural selection affects mean fitness according to the additive variance in fitness associated with allele frequency.

The peculiar part of Fisher's argument is that any change in fitness caused by a change in the average effect of an allele is an environmental effect. Because the average effect of an allele often depends on its frequency, a change in allele frequency caused by natural selection is also a change in the environment. By this formulation, fitness, or a trait correlated with fitness, increases by an exact amount because of natural selection but simultaneously increases or decreases by an unpredictable amount because of the 'environment'. The Fundamental Theorem provides no general statement about evolutionary change.

There is, naturally, a certain disappointment that the theorem says nothing about evolutionary dynamics. Indeed, since the goal of mathematical population genetics is to provide explicit dynamical models, it is not surprising that most authors have assumed that Fisher's theorem was intended to be part of a dynamical theory, or else have expressed disappointment when they realized what Fisher had really done.

What one gains from the Fundamental Theorem, however, is a stronger ecological sense of the relationship between natural selection and evolution: the evolution of

mean fitness, or of a character correlated with fitness, is interesting only in the context of population dynamics. Similarly, the evolutionary significance of changing gene frequency can only be understood in the context of the genomic environment.

Fitness gradients and ecology

Fisher did not question the mathematical validity of Wright's equations. He did, however, question the evolutionary significance of the mean-fitness gradient because it ignores the ecological aspects of evolutionary change.

The gradient approach can incorporate 'genomic ecology' (e.g. epistasis, frequency dependence) and population ecology (density dependence)¹⁹, but the primary use of the gradient for predicting or interpreting the evolutionary consequences of selection has been based on the uncorrected Adaptive Landscape that Fisher criticized.

The tension continues between fitness-gradient and ecological views of evolution. On one side, much of evolutionary quantitative genetic theory and the inferences drawn from measurements of selection in the wild have been based on the mean-fitness gradient. On the other side, Cooke *et al.*'s model shows clearly that measurements of selection on traits like clutch size may be misleading if interpreted outside of their ecological context: a fitness gradient (Adaptive Landscape) is not sufficient to infer evolutionary

history or to predict future changes in traits correlated with fitness.

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References

- 1 Wright, S. (1932) *Proc. Sixth Int. Congr. Genet.* 1, 356–366
- 2 Provine, W.B. (1986) *Sewall Wright and Evolutionary Biology*, University of Chicago Press
- 3 Fisher, R.A. (1941) *Ann. Eugen.* 11, 53–63
- 4 Fisher, R.A. (1958) *The Genetical Theory of Natural Selection* (2nd edn), Dover
- 5 Ewens, W.J. (1989) *Theor. Popul. Biol.* 36, 167–180
- 6 Wright, S. (1988) *Am. Nat.* 131, 115–123
- 7 Fisher, R.A. (1958) *J. Ecol.* 46, 289–293
- 8 Moran, P.A.P. (1964) *Ann. Hum. Genet.* 27, 383–393
- 9 Falconer, D.S. (1981) *Introduction to Quantitative Genetics* (2nd edn), Longman
- 10 Crow, J.F. and Nagylaki, T. (1976) *Am. Nat.* 110, 207–213
- 11 Kimura, M. (1958) *Heredity* 12, 145–167
- 12 Kimura, M. (1965) *Genetics* 52, 875–890
- 13 Nagylaki, T. (1991) *Proc. Natl Acad. Sci. USA* 88, 2402–2406
- 14 Price, G.R. (1972) *Ann. Hum. Genet.* 36, 129–140
- 15 Cooke, F., Taylor, P.D., Francis, C.M. and Rockwell, R.F. (1990) *Am. Nat.* 136, 261–267
- 16 Wright, S. (1949) in *Genetics, Paleontology and Evolution* (Jepson, G.L., Simpson, G.G. and Mayr, E., eds), pp. 365–389, Princeton University Press
- 17 Crow, J.F. and Kimura, M. (1970) *An Introduction to Population Genetics Theory* Harper & Row
- 18 Charlesworth, B. (1980) *Evolution in Age-Structured Populations*, Cambridge University Press
- 19 Barton, N.H. and Turelli, M. (1987) *Genet. Res.* 49, 157–173

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