Journal of Genetics, Vol. 96, No. 5, November 2017, pp. 773–782
https://doi.org/10.1007/s12041-017-0833-4

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Haldane and modern evolutionary genetics

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Published online 24 November 2017

Keywords. allele frequency; evolutionary genetics; Haldane's rule; mutation; natural selection.

Introduction

J. B. S. Haldane is renowned as one of the three 'Founding Fathers' of population genetics, mainly because of his series of papers on mathematical models of selection that were published in the 1920s and early 1930s. He also made many other important contributions to genetics and to other fields, especially biochemistry and physiology. The other two Founding Fathers also did important work outside population genetics—R. A. Fisher in statistics and human genetics, and S. Wright in mammalian and developmental genetics. Like Fisher, but unlike Wright, Haldane was unusual among biologists in having had a sound training in mathematics. He was one of the most erudite figures of the twentieth century, and did not hesitate to display his wide knowledge in his numerous popular essays. He was also famous for his colourful and irascible personality as well as for his Marxism, which represented a (very understandable) revolt against the British upper classes into which he was born. In this essay, I will focus on his main contributions to population genetics and evolutionary biology. This is not an exhaustive survey of Haldane's work in this area; rather, I will examine topics that are still influential in contemporary research. I will discuss some more personal aspects at the end of this article.

Gene frequency change caused by selection

Haldane pioneered the theoretical study of natural selection acting on Mendelian variants in a series of papers starting in 1924. He summarized the main results in the appendix to his 1932 book *The causes of evolution* (Haldane 1932), a wonderfully clear account of genetic aspects of evolution which is well worth reading today. The Afterword by Egbert Leigh to the 1990 Princeton University Press edition of *The causes of evolution* provides an extensive discussion of Haldane's work on population genetics up to 1932, and includes corrections of some mathematical errors (Haldane 1990).

To some extent, this early work was anticipated by the mathematician Harry Norton of Trinity College Cambridge, who presented numerical results on the time taken for the spread of a selectively advantageous mutation in an appendix to the book by R. C. Punnett on mimicry (Punnett 1915), but never published the underlying derivations. Haldane was also a member of Trinity for some time in the 1920s, and is said to have been stimulated to work on population genetics by conversations with Norton (Provine 1971). Norton's then unpublished work on the theory of selection in an age-structured population (Norton 1928) was mentioned in Haldane's 1927 paper on the same subject (Haldane 1927a). Fisher had also previously treated the theory of selection on a single autosomal locus in his 1922 paper, where the maintenance of variability by heterozygote superiority in fitness was described for the first time (Fisher 1922). Since Haldane did not cite Fisher in his first two papers, it seems clear that his work was independent of Fisher's—in contrast to Fisher, he always provided detailed citations of the literature in his papers. Haldane's papers, again in contrast to Fisher's, often included lengthy algebraic derivations. According to John Maynard Smith, Fisher was once heard to refer to 'All that algebra that Jack seems to find necessary'.

His first paper (Haldane 1924a) has been enormously influential. This described formulae for the time taken for selection to change the frequency of an advantageous allelic variantat a single locus, in large populations

reproducing with discrete generations under a variety of genetic systems. These included asexual (haploid) inheritance, random mating with autosomal diploid inheritance (including dominance or recessivity of the effect of the mutation on fitness), and sex-linkage. This paper was followed by one dealing with the effects of partial inbreeding, assortative mating and selective fertilization (Haldane 1924b), and another concerning selection at a single locus with arbitrary dominance as well as selection on a phenotype generated by a combination of alleles at multiple loci (Haldane 1927a).

As Haldane pointed out in the introduction to his first paper 'A satisfactory theory of natural selection must be quantitative. In order to establish the view that natural selection is capable of accounting for the known facts of evolution we must show not only that it can cause a species to change, but that it can cause it to change at a rate which will account for past and present transmutations'. At first sight, it might seem that a new advantageous mutation that is present in only one individual in a large population would need very many generations to spread to a high frequency, possibly of the order of the population size. But Haldane showed that mutations spread much more quickly, except for completely recessive autosomal mutations in a randomly mating population. Since exact solutions to the recursion relations can only be found for some special cases (notably haploidy), Haldane mostly used differential equations as approximations to the recursion equations; these approximations are accurate when selection is sufficiently weak.

He showed that, with haploidy or with diploid autosomal inheritance and an dominant favourable allele, the time taken for an allele to spread between a given initial and final frequency is only logarithmically dependent on the initial frequency of the allele (Haldane 1924a). It is inversely proportional to the selection coefficient s, the increase in fitness to carriers of the mutation, when fitness is measured relative to the value for the initial population. For these cases, the time taken for an advantageous allele to spread from a low to a high frequency is a relatively small multiple (of the order of 10) of $1/s$, even if the population size is very large. Selection can therefore transform the composition of a population over a period that is very short compared with the geological timescale. He used his equation for a dominant autosomal allele to estimate the selective advantage of the famous melanic form of the peppered moth, *Biston betularia*, which increased greatly in frequency in industrial areas of Britain during the nineteenth century. His estimate of $s = 0.33$, based on observed changes in the frequency of the melanic form, was in quite good agreement with later, direct estimates based on mark-recapture experiments (Cook 2003). These results did much to persuade biologists that natural selection is a powerful mechanism of evolutionary change, contrary to widely held views at the time (Provine 1971).

The exception is the case of a completely recessive mutation in a randomly mating population. The extremely low frequency of homozygotes for a rare advantageous allele means that selection is ineffective. Haldane pointed out that this implies that mutations with beneficial effects on their heterozygous carriers are much more likely contribute to evolution than completely recessive mutations, consistent with the fact that the allele causing melanism is dominant. This principle has come to known as 'Haldane's sieve' (Turner 1977), and has stood up very well to later investigations of other cases of recent, human-induced evolution, such as insecticide resistance, where mutations that affect the phenotype of their heterozygous carriers seem to prevail (Bourguet and Raymond 1998), in contrast to the properties of most new mutations.

Haldane also pointed out that this sieve does not apply to populations that reproduce with some degree of inbreeding, or to sex-linkage when advantageous mutations are expressed in the heterogametic sex. The latter observation was influential in the much later development of the theory of the 'Faster-X effect', in which a faster rate of adaptive evolution is predicted for the X (or Z) chromosome compared with the autosomes (Charlesworth *et al.* 1987; Meisel and Connallon 2013). The availability of data on DNA sequence data on within-species variability and between-species divergence has now permitted this prediction to be tested and (in some cases) verified (Meisel and Connallon 2013). Similarly, comparisons of inbreeding and outbreeding species suggest that recessive or partially recessive selectively advantageous mutations are fixed at faster rates in inbreeders than outbreeders (Charlesworth 1992; Ronfort and Glémin 2013).

A weakness of this approach to predicting the efficacy of selection is that a new mutation occurs in the progeny of only a single individual. It is therefore extremely vulnerable to chance loss, even if the population size is large and it has a substantial selective advantage; the deterministic equations apply only when the number of individuals carrying the mutation is sufficiently large that chance loss is improbable. Fisher (1922) applied the method of branching processes to this problem for the case of a very large population with constant size, assuming a mutation that increased fitness relative to wild type by an amount s. Haldane adopted Fisher's approach (Haldane 1927b), and used a Taylor series approximation to show that (with a Poisson distribution of offspring number), the probability of ultimate survival of a mutation is approximately $2s$ if selection is so weak that terms in s^2 can be neglected. When the mutation is unconditionally advantageous, this is also the probability of fixation of the mutation.

In 1930, Fisher applied the diffusion equation method to populations of arbitrary size, and obtained the $2s$ formula for fixation probability as the limiting value as population size increases (Fisher 1930a). Later, Kimura (1964) used the backward diffusion equation method to show that the large population size fixation probability could

be expressed more generally as $2s(N_e/N)$, where N is the size of the breeding population and N_e is Wright's effective population size (Wright 1931, 1938). Haldane also used a heuristic argument to derive the survival probability of a completely recessive mutation as approximately $\sqrt{(s/N)}$ for the case when $N_e = N$, where s is now the selective advantage to homozygotes for the mutation. This shows that a completely recessive favourable mutation has a low chance of survival in a large population. A somewhat more accurate formula, $\sqrt{(2s/\pi N)}$, was later obtained by Kimura (Kimura 1957, 1964).

The formula $2s(N_e/N)$ for the fixation probability of a favourable mutation has been widely used in the field of molecular evolution to predict the rate of substitution of advantageous mutations (Kimura and Ohta 1971; Kimura 1983). One important biological implication is that, even if the same selection pressure is applied to independently evolving populations, different mutations may be involved in adaptation, since it is a matter of chance which mutation first becomes established in the population. This explains, for example, the great diversity of malaria resistance mutations that have spread to high frequencies in different human populations (Kwiatkowski 2005).

In addition, this result can be used to correct for the period of vulnerability to initial loss using the deterministic selection equations. Random events do not change the expected frequency of a mutation, so that an initial frequency q_0 can be replaced in the deterministic equations with the quantity obtained by dividing q_0 by the probability of survival of the mutation (Maynard Smith 1971, 1976). (This is because mutations that have reached the stage when random loss can be ignored have a frequency that is conditional on having survived, and the others have a zero frequency.) This approach has been used in the theory of hitchhiking of neutral variants by a linked advantageous mutation, which plays an important role in contemporary evolutionary genetics for interpreting patterns of variation in natural populations (Barton 2010; Weissman and Barton 2012; Elyashiv *et al.* 2016).

Other contributions to selection theory

Haldane made an important contribution to the theory of selection on a continuous trait that followed the normal (Gaussian) probability distribution, by deriving an expression for the selection differential on the trait (the difference between the trait mean before and after selection) as a function of the proportion of individuals that are allowed to survive to breed under truncation selection (Haldane 1930b). This allowed him to obtain an expression for the selection coefficient on an allele with a small effect on the trait. These formulae have been widely used in the prediction of responses of quantitative traits to selection (Bulmer 1980; Falconer and Mackay 1996). He also showed that truncation selection can lead to selection for increased variability, as well as a change in the mean, a theme which has been taken up recently by William Hill and coworkers (Mulder *et al.* 2007).

As mentioned earlier, Haldane developed the first published model of selection in populations with overlapping generations, assuming continuous time (Haldane 1927a). This requires the use of integral equations to relate the state of the population, as represented by the frequency $q(t)$ of an allele at a locus among the gametes produced at time t, to its state at a range of past times. To obtain a useful approximate expression for the rate of change of allele frequency, he used the first-order approximation $q(t) = q(t) - x\Delta q(t - x)$, where $\Delta q(t - x)$ is the rate of change of allele frequency at time $t - x$. Much later, he applied this approach to a population reproducing over successive, discrete breeding seasons (Haldane 1962), at the request of Bryan Clarke, who was studying selection on the snail *Cepaea nemoralis*. In both cases, provided that population growth is slow and selection is weak, the results implied that the expected life-time reproductive success of an individual could be used in a similar way to fitness in discrete-generation models.

This approach was eclipsed by Fisher's introduction of the 'Malthusian parameter' of a genotype as a measure of fitness with overlapping generations (Fisher 1930b), which apparently provided a simple general way of modelling selection and was much used by Kimura in his work on selection theory, e.g. Kimura (1958). The Malthusian parameter is the rate of growth of log population size of a population with the age-specific mortality and fecundity parameters of the genotype in question. However, there are logical difficulties with the use of the Malthusian parameter when populations have age-structure (Moran 1962, p. 60; Charlesworth 1970); in fact, there is no exact general definition of fitness in age-structured populations (Charlesworth 1994). It turns out that Haldane's method of approximation can be used to relate the life-time reproductive success measure of fitness to the Malthusian parameter approach when selection is weak (Charlesworth 1994). This allows a general treatment of selection theory in age-structured populations, with many applications to the theory of the evolution of ageing and life-histories (Charlesworth 1994).

Haldane also pioneered the mathematical theory of the balance between the inflow of individuals from a 'source' population into a population in which the allele at a given locus that is favoured in the source population is at a selective disadvantage (Haldane 1930a). He showed that the equilibrium frequency of this allele in the recipient is determined by the ratio of the rate of migration and the selection coefficient against it, in much the same way as the case of mutation and selection considered below. A similar model was independently analysed by Wright (1931); much later (Moran 1962, chap. 9), developed a biologically more realistic model, with migration between two populations subject to selection in opposite directions.

The important conclusion is that selection acting in opposite directions in different local populations of a species can cause the populations to diverge in their genetic make-up, provided that selection is sufficiently strong in relation to the amount of migration among populations. This was widely ignored by biologists unversed in population genetics; e.g., Ernst Mayr claimed that the genetic uniformity of a species was maintained by gene flow (Mayr 1963, p. 521). In the 1960s, studies of metal tolerance in plants growing on old mine workings and other situations with abrupt gradients in selection pressures (Jain and Bradshaw 1966) showed that populations were in fact capable of adapting to local conditions in the face of substantial immigration. This convinced the evolutionary biology community that Mayr's view was too simplistic. Haldane was, of course, famously critical of Mayr's dismissal of the utility of population genetic models (Mayr 1959), which he attacked in one of his last papers (Haldane 1964).

Haldane later developed the first analysis of selection varying in direction along a spatially continuous population, generating a 'cline' (geographic gradient) in allele frequency at the locus under selection (Haldane 1948). Here, the strength of migration is described by the standard deviation σ of the probability distribution of the distance moved between birth and reproduction. He suggested that σ could be measured in the field; the strength of selection can then be estimated from the 'width' of the cline. This method has been successfully applied to studies of natural populations (Endler 1977), and several refinements to Haldane's model have been developed (Bazykin 1969; Slatkin 1973; Barton 1979, 1999).

Late in life, after his move to India, Haldane and his student S. D. Jayakar published an influential paper on the theory of selection when the relative fitnesses of genotypes vary in time rather than space (Haldane and Jayakar 1963). They showed that two alleles at a locus can be maintained in the population by selection if the geometric mean fitness of the heterozygote is greater than that of the two homozygotes. They found a more complex condition for a completely recessive allele, which will spread if its arithmetic mean fitness is greater than that of the dominant. Later, John Gillespie extended this model, together with that of spatially varying selection, in his 'SAS-CFF' theory of the maintenance of variability in protein sequences (Gillespie 1991), which he advocated as an alternative to Kimura's neutral theory (Kimura 1983), discussed further below. With the development of methods for surveying genomewide variability at the DNA sequence level, there is increasing interest in detecting signatures of both temporal and spatial variation in selection pressures (Bergland *et al.* 2014). Haldane's theoretical insights form the basis for these approaches.

He also proposed the idea that an interaction between a parasite and a host could lead to negative frequency-dependent selection on resistance of the host to the parasite and on the ability of the parasite to overcome such resistance, leading to polymorphism in both species (Haldane 1949a). This was in the context of a paper emphasising the importance of disease as an evolutionary factor, which is now a major research area in evolutionary biology. Examples of highly polymorphic loci involved in host–parasite interactions are known in plants and animals (Charlesworth 2006). He also seems to have been the first to suggest the idea of what Bryan Clarke later called 'apostatic selection' (Clarke 1969), whereby rare forms of a prey are favoured by frequency-dependent selection because they tend to be overlooked by predators who have formed search images for the prevalent prey type (Haldane 1955a).

Haldane introduced the concept of 'altruistic behaviour' into evolutionary biology, where a behaviour such as an alarm call may harm the individual but benefit other members of the population (Haldane 1932, 1955b). He suggested two processes by which it could evolve. The first was the process of intergroup selection, whereby groups that acquire a genotype promoting the behaviour by genetic drift in opposition to selection within groups out-compete nonaltruistic groups. The second was what is now known as 'kin selection' (Maynard Smith 1964), where altruists benefit their relatives who tend to share the same genotype as themselves. (Both of these ideas were also discussed by Fisher (1930b).) In the hands of William Hamilton (1964a,b) and his followers, the theory of kin selection became a cornerstone of behavioural ecology, providing a crucial framework for relating observations to theory (West *et al.* 2006).

Haldane also anticipated Sewall Wright's 'shifting balance' theory of adaptive evolution (Wright 1932), pointing out that some types of interaction among alleles at two loci create alternative equilibria (Haldane 1930c, 1932). Division of the species into partially isolated populations may allow a process of evolution from an initial equilibrium with lower mean fitness to an alternative with higher fitness, as a result of a 'peak shift' induced by genetic drift, followed by intergroup selection. While Wright repeatedly argued for the importance of this process as a factor in adaptive evolution in a series of papers published throughout his career, Haldane mentioned it only rarely, although he was never as hostile as Fisher to the idea that genetic drift could play a significant role in evolution. The majority of evolutionary biologists today probably believe that the conditions for the operation of the shifting balance process are too restrictive for it to be a major factor (Coyne *et al.* 2000), although it still has some advocates (Wade and Goodnight 2000).

Mutation and the genetic load

Haldane was the first to conduct a mathematically rigorous investigation of the equilibrium between the rate of input of deleterious mutations at a locus and the rate of

their elimination by selection (Haldane 1927b), although a heuristic treatment for dominant mutations had previously been described by C. H. Danforth in 1921 (Muller 1950). In particular, he showed that, in a large randomly mating population, the equilibrium allele frequency of an autosomal mutation that reduces the fitness of its heterozygous carriers by s is approximately u/s, where u is the mutation rate from wild type to the mutant form (this assumes $u << s$); if the mutation is completely recessive, the frequency is $\sqrt{(u/s)}$. Haldane also considered other cases, such as sex-linked mutations. He realized that his formulae could be used to estimate the rates of mutation at loci causing human genetic disorders, provided that estimates of the fitnesses of afflicted individuals were available. The first application was to the X-linked locus at which mutations cause haemophilia (Haldane 1935, 1949b). This 'indirect' method of measuring human mutations was the basis for most mutation rate estimates in humans until quite recently (Vogel and Motulsky 1997); the results (a mutation rate of the order of 10^{-5} per locus per generation) are remarkably close to values that are now being obtained by sequences of the genomes of parents and their offspring (Keightley 2012).

With his characteristic insight, Haldane (Haldane 1949b) saw that the mutation rate estimated for thalassaemia major (beta thalassaemia) using his method (Neel and Valentine 1947) was implausibly high. He therefore proposed that this was a recessive lethal mutation maintained in the population by a selective advantage to the heterozygous carriers, arising from their greater resistance to malarial infection. This interpretation of thalassaemia and other haemoglobin polymorphisms has been amply vindicated by later research (Kwiatkowski 2005).

In another leap of insight, he used data on the inheritance of haemophilia to infer that there was a higher rate of mutation in the male than female germline in humans (Haldane 1947). This has again been validated by later research, with whole genome sequencing of sets of parents and offspring showing that the mutation rate in male but not female gametes increases with age (Keightley 2012; Lynch 2016). This reflects the fact that the number of cell divisions involved in the production of sperm increases with age in male mammals, whereas the eggs are laid down in the female germline before birth (Crow 1997). These findings have important implications for the analysis of patterns of molecular evolution, since the relative mutation rates per generation in males and females, and of X chromosomal, Y chromosomal and autosomal genes are affected by factors such as the generation time and age–structure of the population (Kim *et al.* 2006; Amster and Sella 2016).

Haldane also pioneered the analysis of the effects of recurrent mutation on the mean fitness of a population (Haldane 1937), showing in particular that mutation-selection balance in a large randomly mating population under the assumptions mentioned above leads to a reduction in mean fitness relative to that for a mutation-free population that varies between u (completely recessive autosomal mutations), $3u/2$ (sex-linked mutations), or $2u$ (autosomal mutations with substantial heterozygous effects on fitness). This reduction in mean fitness is now known as the 'genetic load' (Muller 1950; Crow 1958); although Haldane did not use the term, he was unquestionably the pioneer of load theory. (Incidentally, the German word for load, *Belastung*, was used in 1935 by N. W. Timoféef-Ressovsky to describe the presence of recessive mutations in a population, which are revealed after inbreeding (Timoféeff-Ressovsky 1935)).

Haldane also considered the net effect of mutations at a large number of loci under the assumption of independent (multiplicative) effects on fitness, which has subsequently been widely used in many different contexts. This assumption implies that the natural logarithm of mean fitness (measured relative to a mutation-free population) is reduced below zero by the sum of the terms arising from each locus. He used the resulting expressions to estimate the net load caused by recessive lethal mutations in *Drosophila melanogaster*, using data obtained by H. J. Muller with his 'balancer' technique for manipulating whole chromosomes (Muller 1928). Haldane estimated this load as approximately 4%, remarking that 'this may be taken as a rough estimate of the price which the species pays for the variability that is probably a prerequisite for evolution'.

Currently, interest in load theory (with extensions that allow for the effects of genetic drift) has been revived by population genomic data that suggest widespread, but mostly weak, selection on both coding sequences and functional noncoding sequences. Improved estimates of the overall rate of mutation per genome to deleterious alleles also suggest a high rate of input of deleterious mutations into the population—considerably more than one per new zygote in humans (Keightley 2012; Lynch 2016). This has led to debates about how a population's survival can be compatible with the resulting very high load (Kondrashov 1995; Keightley 2012; Lesecque *et al.* 2012; Charlesworth 2013; Barton 2017). Concerns have also been raised that the relaxation of selection against deleterious mutations in humans that is associated with modern life, especially from medical interventions, may lead to an accumulation of slightly harmful mutations over a relatively small number of generations that would reduce the fitness of the population substantially if harsher conditions were to return (Crow 1997; Lynch 2016). Haldane himself drew attention to this problem (Haldane 1941, chap. 4).

In the 1937 paper, Haldane also analysed the case of a locus with a pair of alleles maintained by heterozygote advantage (with a small error in his final expression), and suggested that the fitness loss in this case would select for a duplication that allowed the heterozygote to become fixed

in the population, probably the first time that a mechanism for selecting for duplications had been proposed. A formal model of this was later developed by Spofford (1969), apparently without knowledge of Haldane's proposal.

Haldane returned to the problem of genetic load 20 years later, in his seminal paper on the 'cost of selection' (Haldane 1957), followed by a more exact mathematical treatment (Haldane 1960). Here, he analysed the number of 'genetic deaths' that result from the spread of a favourable mutation from a low initial frequency, q_0. This is equal to the population size multiplied by the cost, C, which is the sum of the load in each generation during the spread of the mutation, where mean fitness is measured relative to that of a population fixed for the mutation. Haldane showed that C is approximately equal to $-\ln(q_0)$ multiplied by a factor of order 1 (its value is 2 for an autosomal mutation with intermediate dominance) under a variety of genetic scenarios; with intermediate dominance and $q_0 = 10^{-6}$, C is approximately 30. Using the multiplicative fitness model, he went on to show that the load per generation resulting from independent substitutions of favourable mutations that are initiated at a rate K per generation across the genome is approximately $1 - \exp(-CK)$; this was later termed the 'substitutional load', L_s (Kimura 1968; Crow 1970). He suggested that a load of 10% might be tolerated by a species, consistent with a rate of substitution of about 1 in 300.

The meaning of C or L_s has often seemed confusing, since it appears paradoxical to assert that natural selection acting on beneficial mutations would reduce the fitness of a population. However, L_s is best thought of as a measure of the *inefficiency* of selection; the fitness of the population is being compared at any one time with the fitness of a population that has the best genotype among all of those currently present in the population (Charlesworth and Charlesworth 2010, chap. 4). Because natural selection does not immediately fix a favourable mutation, the mean fitness always lags behind that of the optimal genotype (Maynard Smith 1976); L_s is a measure of the extent of this lag.

Kimura (1968) extended substitutional load calculations to consider the joint effects of weak selection and genetic drift in a finite population. He used data on the rate of amino acid substitutions in proteins to estimate the net rate of substitution of mutations per haploid genome in humans as about 0.5 per year, and argued that the resulting L_s would be too high for the population to survive, but would be acceptable if mutations were neutral or nearly neutral. This led him to propose that most molecular evolution and variation results from neutral or nearly neutral mutations. This theory has developed into a cornerstone of modern thinking on molecular evolution (Kimura 1983), providing a null model against which alternatives such as substitutions caused by natural selection can be tested. Modern studies using population genomic methods allow estimates of the rates of adaptive substitutions in both coding and noncoding sequences to be estimated, so that a reasonably good empirical estimate of L_s can be obtained. Our own unpublished study of *Drosophila melanogaster* suggests that a typical value of the rate of adaptive nonsynonymous substitutions is 4.3×10^{-10} per nonsynonymous site per generation. There are approximately 14×10^6 nonsynonymous sites in a haploid genome, so the total rate of substitution of beneficial amino acid substitutions is $4.3 \times 10^{-10} \times 14 \times 10^6 = 0.006$, i.e. about one substitution per 166 generations across the genome as a whole. With $C = 30$, we have $L_s = 0.16$, somewhat higher than Haldane's suggested limit. While the substitutional load argument for the neutral theory is dependent on assumptions about the nature of selection that are not necessarily valid (Maynard Smith 1968), it is interesting to see how Haldane's study stimulated its initial development.

Haldane also introduced a method for studying the effect of stabilising selection on a quantitative character on the mean fitness of a population (Haldane 1954), using the 'nor-optimal' model, which assumes that the natural logarithm of fitness falls off in proportion to the squared deviation of the trait value from its optimal value. He used the ratio of the trait's variance before and after selection in a given generation to estimate the constant of proportionality, and hence the load; this lay between 2 to 10% for various traits. This model, which traces back to Karl Pearson (1903), and the resulting estimates of the intensity of stabilising selection, have been widely used in more recent work on evolutionary quantitative genetics (Lande and Arnold 1983; Turelli 1984; Johnson and Barton 2005).

Haldane's rule

For evolutionary biologists who are not interested in the mathematics of population genetics, Haldane's best-known contribution is probably his 1922 paper, formulating what has become known as Haldane's rule (HR): 'when in the offspring of two different animal races one sex is absent, rare, or sterile, that sex is the heterozygous (heterogametic) sex' (Haldane 1922). This generalization has been tested many times subsequently; although there are exceptions, the rule seems to hold throughout the animal kingdom (Schilthuizen *et al.* 2011).

With the resurgence from the 1980s onwards of work on the genetic basis of speciation, led in great part by Jerry Coyne (Coyne and Orr 2004), there has been a huge amount of interest in the causes of HR, and what it tells us about the causes of reproductive isolation between species, the core of the 'biological species concept' that emerged during the Modern Synthesis of evolution (Dobzhansky 1937; Huxley 1940; Mayr 1942). Several hypotheses have been proposed to explain HR. Haldane's own proposal

involved a chromosomal rearrangement between an autosome and the Y chromosome (Haldane 1932, p. 42), but this is not consistent with evidence from many genetic analyses of the basis of hybrid sterility or inviability (Coyne and Orr 2004).

The best supported hypothesis seems to be the 'dominance' model, which proposes that reduced fitness in F_1 hybrids is caused by interactions between alleles at different loci that have originated from the two parental species (Dobzhansky-Muller incompatibilities: DMI). If the deleterious effects of these interactions are partially recessive, then the hemizygous X in males (or Z in females when there is female heterogamety) will fully express the deleterious effects of DMIs, whereas they will be covered up to a greater or lesser extent in females (or in males with female heterogamety) (Muller 1940; Charlesworth *et al.* 1987; Orr and Turelli 2001). As predicted by this model, genetic analyses often reveal disproportionately large effects of the X or Z chromosome on hybrid fertility or inviability. Another contributing factor is the Faster-X effect described above; this would enhance the magnitude of effects of the X (or Z), if the genes concerned are involved in DMIs (Charlesworth *et al.* 1987). Finally, there is considerable evidence for more rapid adaptive protein sequence evolution of genes predominantly expressed in males compared with genes expressed in both sexes or in females; participation of these in DMIs could cause HR in species with male heterogamety but not female heterogamety (Coyne and Orr 2004; Schilthuizen *et al.* 2011). Sorting out the relative contributions of these processes to HR is a thriving current research topic.

Some personal aspects

Haldane died when I was a 19-year old undergraduate, so I had no opportunity of meeting him, although my late mother-in-law was briefly a member of his circle in the early 1930s as a result of her friendship with his student Barnet Woolf (a cofounder of the Cambridge University Communist Party, to which John Maynard Smith later belonged). I remember reading Haldane's poem *Cancer's a funny thing* (whose title is a quotation from W. H. Auden's poem *Miss Gee*) when it was published in the *New Statesman* in 1964, shortly before his death from colon cancer. I had a long association with his eminent student and colleague, John Maynard Smith, spending 10 years at the University of Sussex when John was in his prime there. John was still in awe of Haldane, and nearly always referred to him as 'Prof'. He used to say that he took up theoretical modelling only after Haldane's death, because 'anything I could do, Haldane could do faster'.

John had a large store of anecdotes about Haldane. One of my favourites was Haldane's behaviour at seminars; he used to sit at the front and, if he did not like the way it was going, he would put his large, domed head in his hands and mutter audibly 'Oh God, Oh God'. Needless to say, this was very effective at unnerving the speaker. Haldane also had an unusual technique for dealing with students who wanted to see him. He would be sitting at his desk, immersed in algebra, when the student would knock timidly at the door. No response. A louder knock. No response. Eventually, the student would open the door and peer cautiously in. Haldane would look up, glare ferociously and yell 'God, what do *you* want?'. The student would depart hastily.

Haldane was extremely aggressive, and seems to have been a person who was only happy when receiving a large dose of adrenalin; as he said 'I am a man of violence by temperament and training' (Dronamraju 2009, p. 132). John said that Haldane used to have furious rows with him almost daily. Eventually John plucked up courage, and asked Haldane to stop doing this, as it prevented him from working for a long time after each row; Haldane was astonished that John did not enjoy the rows. This corresponds with what a member of his unit on the front-line in World War I said, in a BBC radio broadcast after Haldane's death; everyone else was scared stiff, and just wanted the whole thing to be over, whereas Haldane revelled in it. According to John, on Haldane's 60th birthday he and his colleagues went to a pub to celebrate. Haldane said that, now he was 60, he could do what he liked. He picked a fight with a sailor who had come into the pub, and knocked him down. The celebration allegedly ended with the participants fleeing down the street with the police in pursuit.

Haldane did not suffer fools gladly, whatever their standing, as exemplified by his famous and very amusing riposte to Ernst Mayr's attack on 'beanbag genetics' (Haldane 1964). Again according to John Maynard Smith, Julian Huxley once gave a rather repetitive talk at a meeting. Haldane got up and said 'You have just proved the Bellman's theorem'. No-one knew what he meant— it was a reference to Lewis Carroll's *The hunting of the snark*, in which the Bellman says 'What I tell you three times is true'.

Haldane unfortunately did not distinguish himself when the facts came to light about the dreadful persecution of geneticists in the Soviet Union under Stalin's direction (at the instigation of T. D. Lysenko), as result of the publication of the August 26, 1948 session of the All-Union Academy of Agricultural Science (Langdon-Davies 1949). In a BBC radio symposium on 30 November 1948, in which he, C. D. Darlington, R. A. Fisher and S. C. Harland (all leading British geneticists of the day) participated, Haldane was the only one not to condemn the actions of the Soviet authorities in suppressing genetics. He confined himself to making statements to the effect that he had not yet had the opportunity to evaluate the claims of Lysenko and his followers. Doubtless his loyalty to the Soviet Union at the time of the start of the Cold War was the cause of this equivocation, but it is a serious blot on his reputation. A stout defence of genetics by an eminent foreign scientist, with known Communist affiliations, might have assisted

those in the Soviet Union who were struggling to save the science from oblivion. However, as pointed out by James Crow in his preface to Krishna Dronamraju's collection of Haldane's popular writings (Dronamraju 2009, p. xx), 'It is fair to say that, although Haldane adhered to his support of Lysenko much longer than most geneticists, he finally gave up. He stopped writing for the *Daily Worker* in 1950 and, although he retained his Marxist views, he ceased his work for the Party and his support of Soviet genetics dwindled'. For a different perspective, both on Haldane's attitude in the matter of Lysenko and on the BBC radio symposium alluded to earlier, see the accompanying article by deJong-Lambert (2017).

Despite these negative aspects of Haldane's personality, John held him in deep affection. He was strongly influenced by Haldane's breadth of knowledge and his ability to write and think clearly, and was highly successful in emulating these traits. In turn, John influenced many of the current generation of elderly evolutionary biologists (including myself), who can therefore be thought of as Haldane's 'grandchildren'. It is to be hoped that some of Haldane's magnificent intellectual heritage has been passed on in turn to his 'great-grandchildren'.

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