

and should facilitate the construction of multiple mutants having a set of desired marker genes. The transfer of the arg_5^- allele into an F^- strain of K-12 has enabled us to map this gene, which prior to this had not been possible because arg_5^- mutants had not been isolated in K-12. Localization of this gene is important for studies of the mechanism of repression in arginine biosynthesis.

It was found that the presence of an Hfr gene excludes the effective transfer of the $Flac^+$ episome during mating. This exclusion resembles the immunity against infection by a temperate phage conferred by the presence of the corresponding prophage.

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SOME GENERALIZED THEOREMS OF NATURAL SELECTION

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Traditional accounts of natural selection usually assume a fixed degree of inbreeding and, especially, that population density exerts no effect on the relative adaptive values of different genotypes. With these assumptions, some very remarkable theorems have been proved, in which fitness plays a major role. Fisher¹ was able to show that, unless the degree of inbreeding varies or the environment deteriorates, the mean fitness always increases; and he gave a formula for the rate of increase. Haldane² showed that, during the course of substituting a superior gene for its allele, the number of genetic deaths (actually $\int (r_{\max} - \bar{r}) dt$, where r_{\max} is the fitness of the most fit homozygote and \bar{r} is the mean fitness of the whole population) is independent of the advantage of the new homozygote over the old. The purpose of this article is to give an account of natural selection which holds for varying degrees of inbreeding and which allows for effects of population density on

fitness. Theorems analogous to those of Fisher and Haldane will be proved, also allowing for density effects.

First, let us describe the replacement of allele y by x . Allowing for effects of total number of individuals on the rates of increase of the genotypes, we can conclude that for each genotype xx , xy , and yy and for each value of p , the proportion of x genes in the population, there will be a value $K_{xx}(p)$, $K_{xy}(p)$, and $K_{yy}(p)$ such that when the combined population of all genotypes equals $K_{xx}(p)$, the birth rate of xx individuals just balances the death rate, and similarly for xy and yy genotypes. Then, as a first approximation which will be quite accurate when the total population, N , is quite near the K values, the excess of the birth rate over the death rate of the xx , xy , and yy genotypes will be proportional to $(K_{xx}(p) - N)$, $(K_{xy}(p) - N)$, and $(K_{yy}(p) - N)$, respectively. This will be precisely true if the genotypes have logistic population control. Now, p is the proportion of x genes: $p = (n_x/N)$, where n_x is the number of x genes in the population; n_y is the number of its allele y . Let $f(p)$ be the proportion of these x genes which, for the given frequency p , are combined in the zygote with another x gene, so that $1 - f(p)$ is the proportion of the x genes which combine with y genes. Let $g(p)$ be the corresponding function for the y genes. Now we can describe the rate of increase of the x genes with respect to time:

$$\frac{dn_x}{dt} = n_x [c_{xx} f(p)(K_{xx}(p) - N) + c_{xy}(1 - f(p))(K_{xy}(p) - N)], \quad (1)$$

where c_{xx} and c_{xy} are constants describing the change in fitness of the xx and xy genotypes which accompanies a unit change in N . Similarly,

$$\frac{dn_y}{dt} = n_y [c_{xy} g(p)(K_{xy}(p) - N) + c_{yy}(1 - g(p))(K_{yy}(p) - N)]. \quad (1')$$

These are accurate in the logistic case, and always a good approximation if the K values are similar. Now we can solve these equations graphically as follows. Suppose, for concreteness, that for all p , $K_{xx}(p) > K_{xy}(p) > K_{yy}(p)$. In Figure 1 we have all the necessary elements for the solution. The coordinates are n_x and n_y (time is not a coordinate). The isoclines $\frac{dn_x}{dt} = 0$, and $\frac{dn_y}{dt} = 0$, which we will call the x -isocline and the y -isocline, are plotted from equations (1) and (1'). Although they are not necessarily straight, the x -isocline must connect $K_{xy}(0)$ on the n_y axis to the point $K_{xx}(1)$ on the n_x axis, and the y -isocline must connect $K_{yy}(0)$ on the n_y axis to $K_{xy}(1)$ on the n_x axis, as the right-hand sides of equations (1) and (1') show. For instance, when $n_y = 0$, $p = 1$ and the right-hand side of equation (1) takes on the value zero only if $N = n_x = K_{xx}(1)$. We now introduce time onto the graphs by plotting a field of arrows which show the direction in which the population is changing. Thus, an arrow pointing down and to the right from the point (n_x, n_y) indicates that a population having n_x of the x genes and n_y of the y genes will change so that the x genes increase in number and the y genes decrease. These arrows are shown in Figure 1, with their directions determined by the isoclines and the meaning of the stippling and cross-hatching. Clearly,³ any sequence of arrows, tail to head, representing the history of any particular population, will always lead

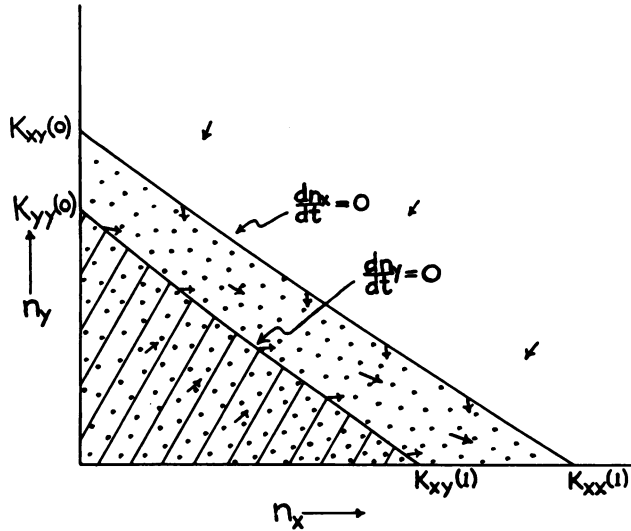


FIG. 1.—Graphical analysis of the replacement of *y* genes by their *x* alleles. n_x and n_y are the numbers of *x* and *y* genes, respectively. $K_{xx}(1)$ and $K_{xy}(1)$ are the densities of the total population such that the *xx* and *xy* genotypes have death rates just balancing birth rates, when $p = 1$. $K_{xy}(0)$ and $K_{yy}(0)$ are defined similarly for the situation $p = 0$. In the stippled area, n_x is always increasing, and in the cross-hatched area n_y is always increasing. Hence in the region with both stippling and cross-hatching, both genes increase, and arrows point up and to the right. In the area with only stippling, n_x increases and n_y decreases, and in the unshaded area, both decrease.

to the point $K_{xx}(1)$ on the n_x axis, for that is the way the whole field of arrows flows. Hence, we have proved that if, for all p , $K_{xx}(p) > K_{xy}(p) > K_{yy}(p)$, then the *x* genes replace the *y* genes. Notice that no assumption of constant degree of inbreeding was needed; we only required that each population composition determine some fixed degree of inbreeding so that the arrows have an unambiguous direction.

Similarly, if $K_{xy}(1) > K_{xx}(1)$ and $K_{xy}(0) > K_{yy}(0)$, then the isoclines cross, and by drawing the graphs, we see immediately that the point of intersection of the isoclines is a stable equilibrium point toward which all arrows converge. This is equivalent to the traditional case of the heterozygote most fit, except that as before, our K values replace the usual fitness or adaptive value terms. Other genetic situations can be handled similarly.

We can now prove theorems resembling those of Fisher and Haldane, mentioned above. Assume that the *x* gene has an isocline only slightly farther out than the *y* isocline, so that the replacement process is slow. Hence $dN/dt = 0$, and $N = \bar{K}$, approximately. We find by differentiating $p = (n_x/N)$ that

$$\frac{dp}{dt} = p \left(\frac{1}{n_x} \frac{dn_x}{dt} - \frac{1}{N} \frac{dN}{dt} \right),$$

which, in our case, becomes approximately

$$\frac{dp}{dt} = p \left(\frac{1}{n_x} \frac{dn_x}{dt} \right) = p c_x \cdot (\text{distance from } x\text{-isocline to } n_x, n_y), \tag{2}$$

where c_x is $[f(p) c_{xx} + (1 - f(p)) c_{xy}]$; c_y is defined similarly. A symmetrical form is

$$\frac{dp}{dt} = p(1-p) \left(\frac{1}{n_x} \frac{dn_x}{dt} - \frac{1}{n_y} \frac{dn_y}{dt} \right) = \quad (2')$$

$$\begin{aligned} & p(1-p) [c_x \cdot (\text{distance from } x\text{-isocline to } n_x, n_y) + \\ & \qquad \qquad \qquad c_y \cdot (\text{distance from } x\text{-isocline to } n_x, n_y)] \\ & = p(1-p) H(p) (\text{distance between isoclines through } n_x, n_y) \end{aligned}$$

where $H(p)$ takes on values between c_x and c_y . Furthermore, since dN/dt is virtually zero, $(r_{\max} - \bar{r})$ is virtually r_{\max} which in turn is $c_{xx}(K_{xx} - N)$. This in turn is nearly $c_{xx}(K_{xx} - \bar{K})$, so the number of selective deaths is virtually equal to c_{xx} times the extra amount of life, measured in animal-hours (or whatever the time unit is), that would have existed had all genes been x . Thus

$$L = \int_{p_0}^{p_f} (r_{\max} - \bar{r}) dt = \int_{p_0}^{p_f} \frac{c_{xx}(K_{xx} - \bar{K})}{\frac{dp}{dt}} dp$$

which, by equation (2) is

$$\begin{aligned} L &= \int_{p_0}^{p_f} \frac{c_{xx}(K_{xx} - \bar{K}) dp}{pc_x \cdot (\text{distance from } x\text{-isocline to } n_x, n_y)} \\ &= \int_{p_0}^{p_f} \frac{c_{xx}(\text{distance from } N = K_{xx} \text{ to } N = \bar{K}) dp}{pc_x \cdot (\text{distance from } x\text{-isocline to } N = \bar{K})} \end{aligned} \quad (3)$$

which precisely equals $\log_e(p_f/p_0)$ when x is dominant, so that $c_{xx} = c_x$, and the x -isocline is the line $N = K_{xx}$. When dominance is not complete, we must assume the line $N = K_{xx}$ is parallel to $N = K_{yy}$, so that (distance from $N = K_{xx}$ to $N = \bar{K}$) equals $(1-p)$ (distance between $N = K_{xx}$ and $N = K_{yy}$). Then, using equation (2'),

$$L = \int_{p_0}^{p_f} \frac{1}{p} \left[\frac{c_{xx}(\text{distance between } N = K_{xx} \text{ and } N = K_{yy})}{H(p)(\text{distance between isoclines})} \right] dp.$$

The term in square brackets is between about 1 and 5, for normal degrees of dominance, so the number of selective deaths is some multiple (Haldane suggested about three) of the number obtained above for the case of complete dominance.

To prove our analogue of Fisher's Fundamental Theorem of Natural Selection, we assume for convenience in exposition that breeding is random. The general case would have additional terms. Then,

$$\begin{aligned} \frac{d\bar{K}}{dp} &= p^2 \frac{dK_{xx}}{dp} + 2p(1-p) \frac{dK_{xy}}{dp} + \\ & \qquad \qquad (1-p)^2 \frac{dK_{yy}}{dp} + 2(pK_{xx} + (1-p-p)K_{xy} - (1-p)K_{yy}) \\ &= \overline{\left(\frac{dK}{dp} \right)} + 2[(pK_{xx} + (1-p)K_{xy}) - (pK_{xy} + (1-p)K_{yy})] \end{aligned}$$

$$= \overline{\left(\frac{dK}{dp}\right)} + 2(\text{distance between isoclines}).$$

Using equation (2'), we obtain

$$\begin{aligned} \frac{d\bar{K}}{dt} &= \frac{d\bar{K}}{dp} \frac{dp}{dt} \\ &= \overline{\left(\frac{dK}{dp}\right)} H(p)p(1-p)[\text{distance between isoclines}] + \\ &\quad 2p(1-p)H(p)[\text{distance between isoclines}]^2. \quad (4) \end{aligned}$$

(The second term can be shown, by a proof like Fisher's, to be $H(p)$ times the additive genetic variance in K .) If the different genotypes do not differentially affect the renewal of the limiting resource, so that the K 's are independent of p , then (dk/dp) is zero and $(d\bar{K}/dt)$ is therefore always positive. On the other hand, if the competing genotypes have different effects on the renewal of the resource (e.g., if one grazes closer), so that $K_{xy}(1) \neq K_{xy}(0)$, then $d\bar{K}/dp$ may even be negative and \bar{K} need not always increase.

Discussion.—In all of these theorems, K values replace the corresponding relative fitness or adaptive value terms of the usual expositions of natural selection. However, because $d\bar{K}/dt$ is not always positive (equation (3)), we enquire what it is that always increases under the action of natural selection. The answer is quite intricate; unless one type of competitor can pollute the resource so that the other type cannot use it, natural selection seems always to decrease the density of limiting resource required to maintain the population at a constant level. But to prove this requires an analysis of a three-dimensional equivalent of Figure 1 in which the third coordinate is the amount of the limiting resource.

Summary.—An account of natural selection is presented which makes no assumption about fixed degree of inbreeding, and which takes into explicit account the effect of population density. Simple analogues of Fisher's Fundamental Theorem of Natural Selection and of Haldane's work on the number of selective deaths during gene substitution are proved. The analogue of Haldane's work also enables us to estimate the number of animal-hours of life which are lost due to poor genotype. In all of these, the carrying capacity of the environment, K , replaces fitness as the agent controlling the action of natural selection.

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