

## The hitch-hiking effect – a reply

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We have no serious disagreement with the mathematical arguments presented by Ohta & Kimura (1975). We do, however, have reservations about their conclusions that 'the hitch-hiking effect is generally unimportant as a mechanism for reducing heterozygosity', and still prefer our own approach (Maynard Smith & Haigh, 1974).

Both papers are concerned with the following problem. There are two linked loci: at one locus there is a pair of neutral alleles  $A$  and  $a$ , and at the other a favourable allele  $B$  is replacing an unfavourable allele  $b$ . How important is the effect of  $B$  on polymorphism for  $A$  and  $a$ ? Haigh and Maynard Smith asked, suppose there is an initial heterozygosity  $h_0 = 2p_A(1-p_A)$  at the neutral locus when the favourable allele  $B$  arises by mutation, what will be the final value of heterozygosity,  $h_f$ , at the  $A$  locus when  $B$  has gone to fixation? The major part (to the bottom of page 321 and Figs. 1-5) of Ohta and Kimura's papers is concerned with a quite different question. They suppose that initially the allele  $B$  is in a state of transient polymorphism, and that a mutation  $a \rightarrow A$  at the neutral locus occurs, linked either to  $b$  or  $B$ . They estimate the expected number of heterozygotes for the allele  $A$  (summed over all generations until  $A$  is eliminated or fixed),  $H_T$ , and ask, how much is  $H_T$  affected by the presence of  $B$ ?

It seems to us that our question is the relevant one, at least in large populations (and it is large populations which are at issue). In a large population, most of the 'neutral' polymorphism will be contributed by alleles which remain in the population for very long periods (of the order of  $N$  generations, where  $N$  is the population size), whereas selectively favourable alleles will go to fixation rather quickly. It follows that it will be much commoner for a selectively favourable mutant to arise closely linked to a pre-existing neutral polymorphism than the other way round.

Ohta and Kimura do tackle what seems to us to be the relevant question on page 322 and Fig. 6. Their treatment differs from ours in that they consider the total heterozygosity,  $H_T$ , at a neutral locus, and calculate the ratio ( $H_T$  with hitch-hiking)/( $H_T$  without hitch-hiking). We estimate the ratio,  $h_f/h_0$ , of the heterozygosity after hitch-hiking to that before. In the absence of hitch-hiking,  $H_T = 2N_e h_0$ . When there is hitch-hiking,  $H_T$  is the sum of  $H$ , the number of heterozygotes occurring during the passage of the favoured allele  $B$  to fixation, and  $2N_e h_f$ , the number occurring after fixation of  $B$ . Thus the Ohta and Kimura ratio  $(2N_e h_f + H)/(2N_e h_0)$  will not differ greatly from ours,  $h_f/h_0$ , if  $H$  is small compared with  $2N_e h_f$ , as may well be the case when  $N_e$  is large.

We would therefore expect their results in Fig. 6 to agree approximately with those given in our paper. It is difficult to make a direct comparison, because their (numerical) results are for an initial frequency of  $B$  of 0.1, corresponding to a very small population, whereas our (analytical) formulae apply only to large populations. However, in so far as it is possible to compare our results, they are similar. More generally, they conclude that the effect is only important when  $c < s$  (i.e.  $A$ - $B$  recombination fraction less than the selective advantage of  $B$ ), and this agrees with our equation (27) that

$$\frac{h_f}{h_0} = \frac{2c \log(1/p_0)}{s(1-R_0)},$$

in which it is the term  $c/s$  which is decisive.

Why then do we disagree about the importance of hitch-hiking? They merely say 'the probability is rather low that an advantageous mutant occurs at a locus so tightly linked to a particular neutral locus that  $c < s$  is satisfied'. This will not quite do, because even rather rare events are important when considering a polymorphism which may last  $4N$  generations. We did make an attempt to estimate the aggregate effect of hitch-hiking, while stating 'this is the most uncertain part of our investigation'. The basic snag is that no-one has any idea of how often a favourable substitution occurs. Our approach was to work with various values of the 'substitutional load'. Even with what seems a rather small value of 1.25 for  $W_{\max}/\bar{W}$ , we found hitch-hiking more important than drift for populations of  $10^6$  or more.

Further, Ohta and Kimura look at the average heterozygosity and find

$$H_T = y_0 H_{T+} + (1 - y_0) H_{T-},$$

where  $y_0$  is the initial frequency of the favoured allele  $B$ , and  $H_{T+}$  is the average total heterozygosity if the new mutant  $A$  is linked to  $B$ . Since  $H_{T+}$  is large when  $y_0$  is small, this averaging process masks the fact that hitch-hiking will, *infrequently*, lead to *large* changes in heterozygosity, and will be 'important'. One such important effect is considered in section 5 of our paper, where the probability of elimination of a selectively maintained polymorphism is investigated.

Thus we agree with Ohta and Kimura that a single hitch-hiking event will only have an appreciable effect on a neutral polymorphism if  $c$  is the same order of magnitude as  $s$ , or is smaller than  $s$ . They conclude from this that hitch-hiking effects are in general unimportant whereas we argued that in aggregate hitch-hiking is more important than drift in large populations. Our conclusion does rest on an assumption about the substitutional load. If substitutional loads are typically much less than 1.25, then our conclusion is wrong. But the difference between their conclusion and ours does not arise because we used a deterministic model, or because we worked with  $h$  rather than  $H_T$ .

REFERENCES

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