

The Hill–Robertson effect is a consequence of interplay between linkage, selection and drift: a commentary on ‘The effect of linkage on limits to artificial selection’ by W. G. Hill and A. Robertson

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Hill & Robertson’s (1966) study is an important one in evolutionary biology. By studying the interplay between linkage, selection and drift at two loci, it led to the discovery of an important biological phenomenon, now called the Hill–Robertson (HR) effect (Felsenstein, 1974). The HR effect establishes that selection at one locus will reduce the effectiveness of selection at other linked loci in finite populations. This has a number of implications in evolutionary biology and has been supported by data from many genomic studies.

Hill and Robertson (1966) studied the probability of fixation of two linked loci under selection following the landmark study by Robertson (1960) that developed a theory for limits to artificial selection in finite populations. Relying heavily on a result obtained by Kimura (1957), Robertson (1960) investigated how selection intensity, the initial frequency of alleles, and population size affect limits to selection. This was initially done for a single locus and was then extended to multiple loci without linkage. The focus of the subsequent paper by Hill and Robertson (1966) is on the effect of linkage on limits to selection.

Using simulation, as the theoretical result was not available for linked loci, Hill and Robertson (1966) observed that selection at one locus will reduce the fixation probability of another locus linked to it, a phenomenon resulting from the interplay of linkage and selection in finite populations. In a way, it can be thought of as a reduction of the effective selection intensity at the linked locus. Tight linkage also slows down the rate of response to selection. Another interesting observation is that there is an excess of repulsion gametes at the selection limit. Selection generates negative disequilibrium between lines at the limit.

Hill and Robertson (1966) explained the reduction of response by linked loci in terms of reduction of effective population size. As explained more succinctly

by Felsenstein (1974), selection at one locus will increase genetic drift at a linked locus by skewing its allelic segregation in the next generation. Alleles associated with a favoured genetic background will tend to leave more offspring, more than would be expected due to direct selection on the locus itself, and alleles associated with a less favoured genetic background will leave fewer offspring. This will increase the drift effect on the locus by reducing the effective population size for the locus, in effect reducing the rate of response to selection and the probability of fixation for the linked locus. The tighter is the linkage, the more significant are the reduction of effective population size and the reduction of response to selection.

The HR effect is similar to Muller’s ratchet (Muller, 1964) that predicts that deleterious mutations will accumulate more readily in a population without recombination (Felsenstein, 1974). Both the HR effect and Muller’s ratchet argue that there is an intrinsic advantage of recombination as it breaks down the negative linkage disequilibrium generated by selection and random genetic drift and thus increases the rate of adaptation. Several other models, such as the hitchhiking model (Maynard-Smith & Haigh, 1974) and the background selection model (Charlesworth *et al.*, 1993; Charlesworth, 1994), also predict that genetic linkage will reduce the levels of neutral polymorphisms, efficiency of selection and rate of adaptation, although different models emphasize different particular selective scenarios.

The importance of the HR effect lies in its explanatory and predictive powers when applied to many observations in evolutionary biology. With the genomics revolution, new lines of evidence have shown that the HR effect could have a detectable influence at a very local and gene-specific level and explain some unexpected patterns of divergence, polymorphism and codon bias in the genome of *Drosophila melanogaster* and other species. Recently, Comeron *et al.* (2008) gave a thorough and excellent review of many studies that have produced evidence

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related to the HR effect at the gene and genomic level. For example, many studies have shown that rates of synonymous evolution increase with the length of coding sequence and levels of synonymous polymorphism are lower in genes with reduced codon bias (Comeron & Aguade, 1996; Moriyama & Powell, 1996; Comeron *et al.*, 1999). Codon usage bias also decreases as the length of coding sequence increases (Moriyama & Powell, 1998; Comeron *et al.*, 1999; Duret & Mouchiroud, 1999). These observations are inconsistent with classical models of weak selection for single sites, but are consistent with the HR effect. More direct evidence comes from comparison of adaptation in different genomic regions with different levels of recombination. Kliman & Hey (1993) first showed a reduced adaptation to optimal synonymous codon usage in genes located in genomic regions with a reduced rate of crossing-over in *D. melanogaster*, a result that has been confirmed more recently by many studies. Also, analysis of the rates of protein evolution between *Drosophila* species has shown that genes located in genomic regions with strongly reduced recombination have an excess of fixed deleterious mutations and a deficit of fixed advantageous mutations as compared with highly recombining genomic regions (Hilton *et al.*, 1994; Takano, 1998; Comeron & Kreitman, 2000).

The HR effect may also explain the evolutionary origin of some structural features of genes and genomes. It has been observed by simulation that neutral regions embedded in regions under selection can reduce the HR effect, thus increasing the rate of evolution (Comeron & Kreitman, 2002). This may suggest that introns could be viewed as modifiers of recombination that reduce an intragenic HR effect, hence providing a possible evolutionary explanation for the origin and maintenance of the intron (Comeron *et al.*, 2008).

Although originally a study of the effect of linkage on the limits of selection, Hill & Robertson's (1966) study yielded some rather unexpected observations that have far reaching implications for the evolution of genes and genomes, and it remains a landmark study in evolutionary biology.

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