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HALDANE'S RULE: A DEFENSE OF THE MEIOTIC DRIVE THEORY

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Two empirical generalizations about speciation remain unexplained: the tendency of the heterogametic sex to be sterile or inviable in F_1 hybrids (Haldane's rule), and the tendency of the X chromosome to harbor the genetic elements that cause this sex bias in hybrid fitness. Recently, I proposed that divergence of meiotic drive systems can explain these two rules of speciation (Frank, 1991, independently put forward by Hurst and Pomiankowski, 1991).

Coyne et al. (1991) have criticized my theory on several counts. I respond to their critique by first showing that my argument is logically sound and that it is not directly contradicted by currently available observations. I then outline several tests of my theory.

Criticisms of the Meiotic Drive Theory

I suggested that divergence of *XY* drive systems can explain Haldane's rule and the role of the *X* in reduced hybrid fitness (Frank, 1991). My argument followed from two assumptions. First, sex chromosomes are particularly susceptible to rapid evolution of meiotic drive systems. Second, divergence of meiotic drive systems can in some cases cause hybrid sterility or inviability.

According to Coyne et al. (1991), my two assumptions are unlikely to be true, and thus my explanation is probably wrong. Their criticisms 1–3 (pp. 1711–1712) address my first assumption, that *XY* drive evolves rapidly, and their criticisms 4–6 (pp. 1712–1713) address my second assumption, that divergence of drive systems can sometimes cause hybrid sterility or inviability. (I assume throughout that males are the heterogametic sex unless otherwise stated.)

1) There may not be a bias in favor of the evolution of XY *versus autosomal meiotic drive systems.*—Our disagreement here arises from different assumptions about the likely mechanisms of *XY* drive.

Their criticism can be stated concisely as follows: The mechanism of autosomal drive is well known in two cases, *SD* and *t*, whereas the mechanism of *XY* drive is unknown. It therefore seems reasonable to assume that the mechanism of *XY* drive is the same as the mechanism of drive in *SD* and *t*. According to this mechanism, potential responder sequences must have been identical on the *X* and *Y* in the ancestral state, before the sex chromosomes became differentiated. If these sequences have remained intact on both the *X* and *Y* and have not diverged, then *XY* and autosomal drive share a common mechanism and evolve at about the same rate. The evolution of *XY* drive is rapid under other assumptions—much more rapid than the evolution of autosomal drive.

My reply to their criticism is: Yes, my model does require some sequence divergence between *X* and *Y*.

Coyne et al. (1991) claim that the *Y* must have a responder for my model to work. This claim is based on the assumption that the mechanism of sex chromosome drive must be the same as in the autosomal systems *SD* and *t*—it is not a general statement about various mechanisms of *XY* or *XO* drive. No *Y* responder is required under the usual models of *XY* and *XO* drive (e.g., Hamilton, 1967; Thomson and Feldman, 1975). Little is known about the actual mechanisms of sex chromosome drive. However, because *X* and *Y* are really different chromosomes rather than paired homologues that constantly exchange genetic material, the mechanism shared by *SD* and *t*, with minor allelic variants occurring at the same responder locus on each homologue, is very unlikely to occur in sex chromosome drive.

2) There may not be a bias in favor of the evolution of suppressors of XY versus autosomal meiotic drive.—Coyne et al. (1991) point out that, although sex-ratio bias is a potent force producing selection for suppressors of *XY* drive, suppressors of autosomal drive may evolve as quickly as suppressors of sex chromosome drive. Whether the statement is true or not, the relative rate of evolution of sex chromosome and autosomal suppressors is irrelevant for my theory. I require only that suppressors of sex chromosome drive often evolve moderately rapidly. The key point is that diverged species *sometimes* become diverged at interacting *X*-linked and autosomal loci.

3) There is little evidence for the differential fixation of meiotic drive genes in related species.—Coyne et al. (1991) ask: Why, if divergence of meiotic drive systems explains sex-biased hybrid incompatibilities, do crosses between species rarely exhibit meiotic drive?

This is a legitimate question. I give one answer in my response to criticism 6 (see below). Here I propose a different explanation.

Sterility and inviability represent loss of function that can be caused by disruption of any one of many pathways. A drive phenotype disrupts a few pathways, causing, for example, death of *Y*-bearing sperm, while preserving nearly identical pathways in the development of *X*-bearing sperm. Drive, with its requirement for protecting and destroying nearly identical pathways, is an adaptation finely tuned to minor DNA sequence variations within a population (Wu and Hammer, 1990). Drive-related sequences are under intense coevolutionary pressure (Frank, 1991). Divergence among populations, causing a disruptive phenotype (sterility) in hybrids, is not surprising. Divergence among populations, causing a delicately balanced drive phenotype preserved in hybrids, may be unlikely. I will return to this point later when I discuss ways to test my theory.

My model of rapid coevolution implies that autosomal suppressors or immune responders often appear quickly on an evolutionary time scale. In support of this rapid evolutionary response, I cited some cage experiments by Lyttle (1979) showing that suppressors rapidly accumulated and reduced the strength of *Y* drive. Coyne et al. (1991) comment that, in Lyttle's cages, there was "a reduction of only 16% in the amount of distortion" in three years. I find this a truly remarkable statement. A change of 16% in three years is a very rapid rate of evolutionary change.

4) It is difficult to see how the divergence of drive systems could produce hybrid sterility.—Coyne et al. (1991) propose three separate criticisms under this heading.

(a) Known drive systems have nothing to do with meiosis. Coyne et al. (1991) claim that, in known drive systems, dysfunction occurs post-meiotically. However, Zimmering et al. (1970, p. 429) remark that, in *Drosophila,* "some instances [of drive] are associated with cytologically observed meiotic irregularities such as . . . the degeneration of the *Y* in *sr* males [*D. obscura* group], while in others such as *SD* [*D. melanogaster*] . . . meiosis is normal." Clear descriptions of meiotic abnormalities associated with *sr* drive can be found in Novitski et al. (1965) and Cobbs et al. (1991).

Coyne et al.'s point here appears to be that one cannot extrapolate from, on the one hand, the particular pathologies observed in any single case of drive within a population to, on the other hand, a general mechanism for how divergence of drive loci causes hybrid sterility. This is certainly true, especially since the cytological pathologies of drive differ from one species to another (Zimmering et al., 1970). I regard the fact that pathologies differ as evidence that there are many mechanisms by which gamete formation can be disturbed and thus many ways by which sterility can result.

(b) Sterility is an unlikely result of incompatibilities at drive loci. Coyne et al.'s point here is that, because they were not aware of any evidence linking drive incompatibilities to sterility, then sterility must be an unlikely outcome of drive incompatibilities. However, soon after Coyne et al. (1991) submitted their critique, Cobbs et al. (1991) demonstrated that incompatibilities at drive loci do in fact cause sterility in *Drosophila pseudoobscura.*

Briefly, these are the details from Cobbs et al.'s study. The *SR X* chromosome causes drive against the *Y* in *D. pseudoobscura.* An interaction between the *SR X* chromosome and autosomal loci in the *L116* strain of *D. pseudoobscura* causes male sterility because of abnormal chromosome pairing during meiosis and extensive spermiogenic failure. The *L116* strain in the absence of *SR X* is normal; *SR X* in the absence of *L116* autosomes causes meiotic drive because only *Y* bearing sperm fail. Thus, incompatibilities between a driving sex chromosome and autosomal loci can cause sterility. The particular genetics of this system cannot apply directly to hybrid sterility, however, because the *L116* autosomes must be homozygous for sterility to occur. But the point is only that sterility is a plausible outcome, not that this particular mechanism is a general one.

In my original article, I suggested that Hartl's (1973) study of autosomal drive in *D. melanogaster* provided evidence that divergence among drive systems could cause sterility. Coyne et al. (1991) show clearly that I misinterpreted Hartl's study, and that this study has no bearing on the relationship between divergence and sterility.

(c) Rare cases of hybrid female sterility cannot be explained by my theory. These cases are indeed a difficulty for my theory without adding further ad hoc assumptions.

5) It is difficult to see how the divergence of drive systems could produce hybrid inviability.—My theory provides no clear and compelling explanation for sex-biased hybrid inviability. This is a weakness that my theory shares with other attempts to explain Haldane's rule (e.g., Coyne and Orr, 1989). My theory can be saved by further assumptions; I discuss these assumptions in a later section.

6) Frank's model predicts that autosomal suppressors are semidominant, which is a problem when explaining hybrid sterility.—This criticism shows why meiotic drive may be rare in hybrids, but it does not diminish the likelihood that sterility or inviability result from hybrid incompatibilities. To see this, I summarize the argument in Figure 2 of Frank (1991).

Suppose the ancestral genotype of a species pair is *XO AA,* and one of the current species evolves to a genotype of *X'O A'A'*, where *X'* is a driving *X* in the absence of *A'*, an autosomal suppressor of drive. The hybrids are *XO AA'*, with an unpredictable phenotype (perhaps sterile), and *X'O A'A*. Since suppressors are semidominant, this latter hybrid has a normal phenotype because the driving *X'* is suppressed by *A'*. The semidominant nature of autosomal suppressors may explain one of Coyne et al.'s main criticisms (3 above): if meiotic drive systems often diverge, then why do hybrids fail to have distorted segregation ratios?

Now suppose that there is a second coevolutionary event in the meiotic drive system of either species. As an example, let the pristine species evolve from *XO AA* to *X*O A*A**. The hybrids are now *X*O A'A** and *X'O A*A'*. The dominance relationships between *A'* and *A** are unpredictable, since these alleles have never met before. Likewise, the phenotypes are unpredictable. Sterility or inviability caused by *X-A* incompatibilities are certainly possibilities.

Tests of the Meiotic Drive Theory

Tests proposed by Coyne et al. (1991)—Coyne et al. propose five tests of my theory (p. 1713). Their predictions 1–3 do not follow from my theory, as explained in my response to their criticism 1 (see above). I discuss how to test aspects of their prediction 4 below. Observations related to their prediction 5, regarding *X* effects in the homogametic sex, are not explained by my theory without further ad hoc assumptions and deserve further attention. These observations do not, however, directly contradict a prediction of my theory.

Divergence of drive.—The assumption that divergence of sex chromosome drive systems occurs sufficiently often to explain Haldane's rule would be falsified if both of two conditions hold: (a) Sex chromosome drive is rarely observed in hybrids. Coyne et al. cite evidence suggesting that this is the case. (b) If a drive system has diverged between two parental stocks, then drive will be observed in the hybrids. If (b) is false, then data for condition (a) cannot be used to test the theory. An extension of Lyttle's cage experiments would be the best way to test (b). See Frank (1991) for a description of these experiments and references.

I emphasize laboratory experiments because there is an ascertainment problem for testing (b) with hybrids between natural populations. Suppose that one rarely finds cases in which drive occurs in hybrids but drive does not occur in either parental stock. There is no way to know how often: (1) drive systems have diverged; (2) drive is not expressed in either parental strain; and (3) in hybrids, either sterility or normal phenotypes are observed.

Sterility or inviability caused by drive.—The meiotic drive theory would be falsified if crosses between parental stocks with diverged *XY* drive systems rarely resulted in sex-biased sterility or inviability. Again, extensions of Lyttle's cage experiments are promising, because the causal role of drive can be tested directly if hybrids between separate cages did show reduced fertility or viability.

Data from natural populations once again pose a problem of interpretation. The theory predicts that sex-biased hybrid sterility and inviability are caused by divergence of drive, not that divergence of drive necessarily causes sterility or inviability. Data from natural populations that showed sufficiently diverged drive systems (see Frank, 1991, Figs. 1 and 2) but no hybrid drive, sterility, or inviability, would be difficult to interpret without a large sample size.

Identification of hybrid sterility genes.—The theory would be falsified if, in several cases, the major genes causing sex-biased sterility or inviability are identified and their gene products or DNA sequences have nothing to do with meiotic drive. One complication, not discussed previously, is that divergence of drive often causes divergence of linked loci. Thus drive can play a role even if the drive loci themselves do not cause

sterility or inviability. This corollary is, in general, untestable, because phantom drive systems can be invoked for any hybrid aberration. I have therefore avoided the role of linked loci in developing my theory. An extension to Lyttle's cage experiments may, however, provide some insight into this problem. For example, drive systems diverging between cages may, by greatly accelerating the divergence of linked loci, indirectly cause reduced fertility or viability in hybrids between cages. If so, then further tests for phantom drive loci would have to be designed, focusing particularly on viability effects, since these effects are the greatest challenge to the theory.

Conclusion

Coyne et al. (1991) presented a long list of criticisms. In this reply I have demonstrated that none of the criticisms of my logic stand, and that there are no clear contradictions between the known facts and my theory. Thus my theory remains plausible after intense scrutiny.

My model will have contributed significantly if, on the one hand, it encourages more tests along the lines of Lyttle's cage experiments, extending knowledge about the evolutionary dynamics of meiotic drive, and, on the other hand, it sharpens the specification and testing of competing theories. If my model also explains Haldane's rule, then it will have solved one of the outstanding puzzles of evolutionary biology.

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