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SHORT COMMUNICATION

Synergistic epistasis and alternative hypotheses

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Abstract

Inbreeding generally results in deleterious shifts in mean fitness. If the fitness response to increasing inbreeding coefficient is non-linear, this suggests a contribution of epistasis to inbreeding depression. In a cross-breeding experiment, Salathé & Ebert (2003. *J. Evol. Biol.* **16**: 976–985) tested and found the presence of this non-linearity in *Daphnia magna*. They argue that epistatic interactions cause this non-linearity. We argue here that their experimental protocol does not allow disentangling the effect of synergistic epistasis from two alternative hypotheses, namely hybrid vigour and statistical non-independence of data.

Salathé & Ebert (2003) recently presented in this journal the results of an experiment on the genetic architecture of inbreeding depression. They examined the relationship between inbreeding level and phenotypic value in the parthenogenetic crustacean *Daphnia magna*. Their main result was a decline of fitness-related characters with the inbreeding coefficient at a greater than linear rate. The authors interpreted this result as evidence that deleterious mutations at different loci interact synergistically.

Our purpose here is not to dispute that synergistic epistasis could explain the results obtained by Salathé & Ebert (2003). Rather, we argue that at least two other processes could lead to the same results, namely the hybrid vigour and the non-independence of data. As hybrid vigour is certainly the most important one, it is considered first.

Salathé & Ebert (2003) obtained three classes of increasingly inbred genotypes (Fig. 1). The genotypes with the two lowest levels of inbreeding G_{2x} ($F \geq 0.25$) and G_{3x} ($F \geq 0.5$) were derived from a cross between clones from two different subpopulations (P_s and P_x). G_{2s}, the genotype with the highest inbreeding coefficient ($F \geq 0.75$), was obtained by two generations of selfing of the clone from the P_s subpopulation. Therefore, G_{2s} genotype differs from G_{2x} and G_{3x} not only by its inbreeding coefficient, but also by its genetic background: G_{2x} and G_{3x} are constituted by a mix between two genomes (P_s and P_x), whereas G_{2s} is made of genes from P_s only. In this context G_{2x} and G_{3x} could benefit from hybrid vigour whereas G_{2s} cannot. Enhanced fitness is well known to occur after several types of crosses between (sub)populations, including F_1, backcrosses, F_2, etc. (Lynch, 1991; Falconer & Mackay, 1996; Burke & Arnold, 2001 and references therein). And indeed, Ebert *et al.* (2002) have recently demonstrated that very strong hybrid vigour is present in populations of *D. magna* from southern Finland, the area where the parents of the crosses discussed here are coming from.

We therefore argue that the non-linear response of fitness observed could result from a fitness advantage of

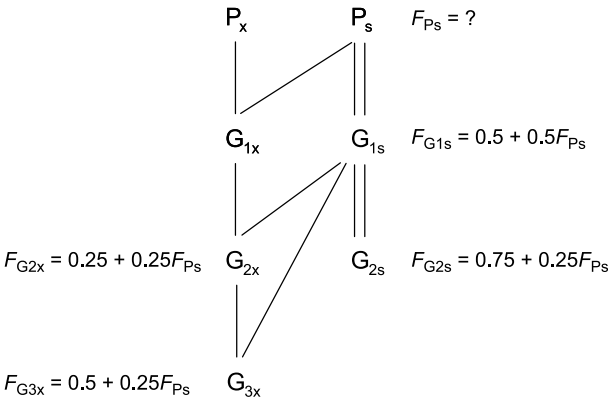

Fig. 1 Experimental protocol used in Salathé & Ebert (2003) and inbreeding coefficient of the different genotypes. Figure modified from Salathé & Ebert (2003).

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G_{2x} and G_{3x} due to hybrid vigour. This genetic process is usually attributed to different deleterious mutations randomly fixed in the different populations (a phenomenon termed drift load: Whitlock *et al.*, 2000; see Keller & Waller, 2002 for review) and to the net masking of their deleterious effects in among-population crosses. It could be argued that hybrid vigour is simply inbreeding depression in reverse. But additive by additive epistasis can contribute to hybrid vigour (Lynch, 1991), while inbreeding depression only occurs if some form of dominance (with or without epistasis) is present (Lynch & Walsh, 1998, p. 258). Therefore inbreeding depression and hybrid vigour can have a different genetic basis and cannot be considered as the same phenomenon.

A way to test the existence of hybrid vigour in the experimental design of Salathé & Ebert (2003) would be to examine the effects of within and between-subpopulation crosses on the relative performance of the progeny. These comparisons of fitness would need to be performed on progeny with equivalent inbreeding coefficients in the two types of crosses. If offspring from between-subpopulation crosses show higher fitness compared with offspring issued from crosses within subpopulations, this could confirm that the mix between two genomes may enhance fitness in G_{2x} and G_{3x} genotypes.

Another explanation for the results observed by Salathé & Ebert (2003) has to do with the non-independence of data (Lynch & Walsh, 1998, p. 262). In the protocol they used, G_{3x} is a genotype directly derived from G_{2x}. Indeed a backcross between G_{2x} and G_{1s} gave G_{3x}. As these two data points (G_{2x} and G_{3x}) are based on individuals that are descendants of each other, their fitness is therefore not independent, and this might partly explain their similar values. An associated issue is that the non-independence of data creates a statistical problem: a basic assumption underlying ANOVA (the test used in their study) is violated.

Lynch & Walsh (1998, p. 265) suggest directions for alleviating this problem of non-independence of data. The general idea is based on crosses of various classes of relatives to obtain simultaneously independent lines inbred to differing degrees. Furthermore, if the crosses are performed within (sub)populations, one can avoid the confounding effect of hybrid vigour.

In conclusion, we do not dispute that synergistic epistasis is a potential explanation for the non-linearity in the data observed in Salathé & Ebert (2003), but in the light of the previous work carried by Ebert *et al.* (2002), we feel that hybrid vigour is an explanation as likely as is synergistic epistasis.

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