LETTERS

Sexual reproduction selects for robustness and negative epistasis in artificial gene networks

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The mutational deterministic hypothesis for the origin and maintenance of sexual reproduction posits that sex enhances the ability of natural selection to purge deleterious mutations after recombination brings them together into single genomes[1]. This explanation requires negative epistasis, a type of genetic interaction where mutations are more harmful in combination than expected from their separate effects. The conceptual appeal of the mutational deterministic hypothesis has been offset by our inability to identify the mechanistic and evolutionary bases of negative epistasis. Here we show that negative epistasis can evolve as a consequence of sexual reproduction itself. Using an artificial gene network model[2,3], we find that recombination between gene networks imposes selection for genetic robustness, and that negative epistasis evolves as a by-product of this selection. Our results suggest that sexual reproduction selects for conditions that favour its own maintenance, a case of evolution forging its own path.

A century of genetic research has revealed two general properties of spontaneous mutations with detectable effects on fitness: most of them are deleterious, and they frequently interact with each other[4,5]. Many types of interactions are possible, including directional epistasis, in which the average effect of spontaneous mutations changes in the presence of other mutations in the genome[6]. Directional epistasis can be either negative (synergistic) or positive (antagonistic), depending on whether the average effect of mutations becomes more or less harmful, respectively, as the number of other mutations in the genome increases (Fig. 1). Directional epistasis holds particular interest for evolutionary biologists because it is expected to determine the outcome of multiple evolutionary processes, notably the evolution of sex and recombination[1]. Empirical studies on a variety of organisms have reported every conceivable form of directional epistasis: negative[7–9], positive[6,10] and no significant directional epistasis[11,12]. These mixed results have not helped to clarify either the mechanistic or evolutionary causes of directional epistasis[13].

In contrast, evolutionary simulations using computational models of RNA secondary structure[14], viral replication[15] and artificial life[14] have demonstrated that the average strength and direction of epistasis can be shaped by natural selection. One mechanism by which epistasis evolves in these models[13] is through a negative correlation among genotypes between the extent of genetic robustness (or genetic canalization, measured as the insensitivity of a phenotype to mutation) and the direction of epistasis. As a consequence, selection for higher robustness produces a correlated response in the strength of epistasis in all three models, towards either weaker positive or stronger negative epistasis[14,15]. The repeatability of this result in models of different biological systems suggests that the strength and direction of epistasis observed in living organisms depend on their history of selection for genetic robustness.

Theory predicts that traits can evolve to be robust to genetic perturbations (that is, mutation and recombination) under a variety of selective regimes[16–18], as long as the following two conditions are met: genes must interact to determine the trait[17–19], and the population must contain sufficient genetic variation[18]. Whereas the former condition is inherent to particular organisms, the latter condition will depend on population genetic parameters such as the mutation and recombination rates. Experimental tests of these predictions using computational models confirm that high mutation rates, such as those experienced by RNA viruses, favour the evolution of genetic robustness[2,3,18,20]. Sexual reproduction (that is, increased recombination) is also expected to impose stronger selection for genetic robustness than asexual reproduction[21,22], but this hypothesis has never been tested experimentally[21].

To test this hypothesis, and to determine whether the evolution of genetic robustness is accompanied by the evolution of negative epistasis, we return to the computational model of genetic networks used in two previous studies[2,3]. We chose this model primarily because it explicitly incorporates one of the key characteristics required for the evolution of robustness[17–19]—genetic interactions. Furthermore, empirical data from biological systems has consistently suggested that extant gene networks are robust to changes in biochemical rate parameters and levels of gene activity[19,23]. Previous work with this model has shown that genetic robustness (again, measured as robustness to mutation) evolves readily if networks are subjected to selection for the production of a stable gene expression pattern[2,3]. Here we explore the extent to which recombination contributed to the evolution of genetic robustness in this model, and ask whether recombination, through its effect on robustness[2,21,22], can cause the direction of epistasis to evolve.

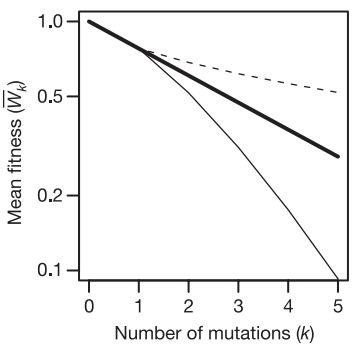

Figure 1 | Types of directional epistasis for deleterious mutations. Three hypothetical relationships between fitness (log scale) and number of deleterious mutations are plotted. All relationships depicted have the same mutational robustness ($\overline{W}_1 = 0.78$) but different directions of epistasis: negative epistasis (plain line, concave downwards; $1 - \beta < 0$), no directional epistasis (bold, straight line; $1 - \beta = 0$) and positive epistasis (dashed line, concave upwards; $1 - \beta > 0$).

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