Note

Mutation Accumulation, Soft Selection and the Middle-Class Neighborhood

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ABSTRACT

The "middle-class neighborhood" is a breeding design intended to allow new mutations to accumulate by lessening the effects of purifying selection through the elimination of among-line fitness variation. We show that this design effectively applies soft selection to the experimental population, potentially causing biased estimates of mutational effects if social effects contribute to fitness.

BECAUSE mutations shape adaptation, there is much interest in describing the distribution of effects of *de novo* mutations on phenotypes. Mutation-accumulation experiments are performed to estimate these mutational parameters. Geneticists employ at least three different approaches to accumulate naturally occurring mutations by mitigating the effects of purifying selection: inbred lines (VASSILIEVA and LYNCH 1999; LYNCH *et al.* 2008), balancer chromosomes in Drosophila (MUKAI *et al.* 1972; HOULE *et al.* 1994), and the "middle-class neighborhood" (MCN) breeding design (SHABALINA *et al.* 1997). The last approach applies extreme and invariant bottlenecks ($N = 2$) to each replicate full-sib family at every generation. It is given its name to suggest the mythical lack of reproductive variation among human families of intermediate socioeconomic rank.

The MCN approach was motivated by a desire to accumulate mutations on genetic backgrounds uncompromised by "weak, genetically altered chromosomes" used by alternative approaches (SHABALINA *et al.* 1997). Selection on individual phenotypes was expected to be reduced because at every generation, every full-sib family was sampled for new individuals exactly twice (one male and one female)—thereby eliminating among-family variation for fitness. Sampled individuals were crossed among families to avoid inbreeding. This method of mutation accumulation has become popular over the past decade (*e.g.*, BRYANT and REED 1999; MACK *et al.* 2000; YAMPOLSKY *et al.* 2000; RADWAN *et al.* 2004; ROLES and CONNER 2008).

In the MCN, the fitness of an individual is its probability of being selected for breeding (one per sex per family). Obviously this probability depends upon the survival of the focal individual, but it also is affected by the frequency with which its siblings survive, meaning that its fitness is frequency-dependent. Fitness is also density-dependent. For example, an individual from a highly productive group is less likely to be bred than if it came from a less productive group. Thus, the MCN design is a form of soft selection, or density- and frequency-dependent selection such that there is no variation in fitness among groups (WALLACE 1968, 1975; WADE 1985). Significantly, GOODNIGHT *et al.* (1992) interpreted soft selection in the context of multilevel selection. This perspective views the group-mean fitness as the sum of two components: (1) the individuals' contributions toward their own fitness averaged over all group members and (2) any contextual, or group-level, contributions to the group-mean fitness. The latter includes selection on effects arising from social interactions. GOODNIGHT *et al.* (1992) showed that soft selection is a particularly interesting case of multilevel selection because the condition that all groups have the same fitness requires that individual- and group-level selection have equal but opposite effects on total selection. Below, we show how this perspective reveals problems with how the results of MCN experiments may be interpreted if group-level effects caused by social interactions contribute to fitness in control populations.

We assume that the MCN leaves the social structure of the population intact, ensuring that selection on group-level effects is not affected by the experiment design (group-level selection is the same in the control and MCN populations). For example, if full-siblings were

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TABLE 1

Changes in individual-level selection that result from the application on the MCN breeding design

Multilevel selection components	Changes in individual-level selection	
$g > -i > 0$ or $g < -i < 0$	Intensified	No change
$i > -g > 0^a$ or $i < -g < 0^a$	Reduced	in direction
$g > i > 0$ or $g < i < 0$	Intensified	Reversed
$i > g > 0$ or $i < g < 0$	Reduced	direction

The MCN breeding design is intended to decrease the strength of selection. Although this is always true in the absence of group-level selection, this design may cause individual-level selection to increase or change direction in the general case of multilevel selection. The change in individual-level selection (right columns) follows from the components of multilevel selection prior to the start of the experiment (left column). Components are g, group-level selection on productivity, and i, individual-level selection on productivity. Following the contextual analysis literature (see references in the text), these are defined statistically in terms of partial covariances of relative fitness. The partial covariance between relative fitness and a family-level trait mean $\bar{z}$, holding individual trait values z constant, is group-level selection, $g = \mathrm{cov}(\tilde{w}, \bar{z} \cdot z)$. The partial covariance between relative fitness and an individual-level trait holding the family-level trait mean constant is individual-level selection, $i = \mathrm{cov}(\tilde{w}, z \cdot \bar{z})$. Soft selection, as enforced in the MCN, requires that $i = -g$.

^{a} The initial selection component values that yield changes consistent with the original intentions of the MCN model.

raised interacting with their mothers and their siblings before the experiment, then the same maternal and sib-social effects are also acting during the MCN experiment. Applying GOODNIGHT *et al.*'s (1992) findings to the MCN shows us that the strength of individual-level selection will change. SHABALINA *et al.* (1997), who ignore group-level selection, expect that the strength of individual-level selection will be reduced and more deleterious mutations will accumulate. In fact, this change can be very different depending upon the strength and direction of group-level selection relative to individual-level selection *prior* to the application of the MCN. When group-level selection is initially stronger, for example, the *intensity* of individual-level selection will increase because the parity conditions of soft selection require it to do so. When the two levels of selection act in concert, the MCN will cause the *direction* of individual-level selection to reverse. Both types of change can happen simultaneously: if group-level selection is relatively stronger but in the same direction as individual-level selection, then the MCN will cause individual-level selection to change direction and become more intense. Table 1 describes how these changes follow from the initial components of multilevel selection.

For example, let us consider how the MCN will change multilevel selection when group- and individual-level components of selection are in initially in conflict

$(g > 0 > i)$. Let us also assume that group-level selection is equal to individual-level selection times some factor $-1/r$, where r is "relatedness," or the proportion of phenotypic variance that exists among groups. These are the well-known threshold conditions necessary and sufficient for selection to favor the persistence of an altruistic trait (*i.e.*, Hamilton's rule—see HAMILTON 1964, 1970; WADE 1980), or $gr = -i > 0$ (this corresponds to the entry in the first row of Table 1). In principle, the MCN will not change the group-selection component. However, because soft selection requires that $i = -g$, individual-level selection must change by $\Delta i = -g(1 - r)$. For the simple case of groups defined by random-mated full-sib families $(r = \frac{1}{2})$, the MCN will double the strength of individual-level selection. Heritable variation for the trait will permit the intensified individual-level selection to change the phenotype even in the absence of new mutations.

If we view such a response to selection from a perspective that ignores multilevel selection, then we will attribute phenotypic change to the cumulative effects of mutation. The risk is that if soft selection causes individual-level selection to change, then a response to selection will be falsely attributed to mutation accumulation. Let us imagine, as before, that individual-level selection is made more intense. The phenotypes will change in such a way as to increase individual-level fitness, causing us to believe mistakenly that mutations were actually beneficial. Alternatively, suppose individual-level selection was reversed. The phenotypes would then deteriorate rapidly because individual-level selection would be forced to act in a direction counter to how we have perceived fitness. Here, the deleterious effects of mutations would be overstated, especially since reverse selection is believed to cause more rapid responses than selection that is applied in the original direction (FALCONER and MACKAY 1996).

We see that the MCN will function as originally intended under a rather limited region of parameter space. Of course, this does not necessarily mean that these conditions are rare. Fortunately, multilevel selection components can be estimated using contextual analysis (HEISLER and DAMUTH 1987; GOODNIGHT *et al.* 1992; FRANK 1997; OKASHA 2004) to evaluate the applicability of the MCN approach before the experiment begins. If conditions preclude using the MCN, then another method, such as inbreeding or balancer chromosomes, should be considered in designing an experiment to measure mutational distributions.

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