

NEWS AND COMMENTARY

Population genetics

Peak shifts in large populations

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Researchers have modelled a new mechanism by which populations can navigate an adaptive landscape. Where a previous model was limited to illustrating how small populations might move from one fitness peak to another, this new model elucidates how large populations might do the same.

In the 1930s, Wright (1931, 1968) proposed that organisms should be thought of as living on an 'adaptive landscape'. In this metaphor, he envisioned a surface where position was defined by underlying genetic (and presumably epigenetic and environmental) factors. The 'height' of the surface was a measure of fitness. He imagined that particularly favorable genotypes would correspond to adaptive 'peaks' that were separated from other such peaks by 'adaptive valleys', or combinations of genes that were not favorable. Wright posed the question of how a population could move from a lower adaptive peak to a higher adaptive peak if in doing so it had to cross an adaptive valley. His solution was to invoke genetic drift acting in small populations. Until now this has been accepted as the primary mechanism for crossing these adaptive valleys. That may all change, since Weinreich and Chao (2005)'s recent model of a convincing mechanism by which peak shifts can occur in large populations.

Weinreich and Chao modeled a haploid two locus genetic system with an A locus (with A and a allele) and a B locus (with B and b alleles). In their system ab genotypes have intermediate fitness, Ab and aB genotypes have low fitness, and AB genotypes have high fitness. Thus, populations fixed for the a and b alleles are at an intermediate fitness peak, while populations fixed for the A and B alleles are at a high fitness peak, with the two peaks separated by low fitness valley due to the transitional (aB and Ab) genotypes. In a system such as this the relevant question is how can a population at the intermediate fitness peak cross the fitness valley to the high fitness peak.

In Wright's original model (1931), he discussed the probability of peak shifts

occurring, and decided that the most likely scenario was that genetic drift in small populations would lead to the chance fixation of transitional genotypes. Thus, a population fixed for the ab genotype might be envisioned to have a mutation from a to A, and then by random genetic drift the Ab low fitness genotype would be fixed. Subsequently, if a B allele were introduced either by mutation or migration it would rapidly increase leading to the fixation of the AB genotype.

There are a number of problems with this scenario. The chance of a mutation from a to A occurring is small, and the absolute number of such mutations will be very small in small populations. However, it is only in small populations that there is any chance that drift will be able to dominate over selection. Thus, this model finds itself in the dilemma of needing both moderate to large population size to generate the variability needed for the peak shift to occur, and the small population size needed to allow drift to dominate over selection. The standard solution to this problem is to postulate that the species is divided into a 'metapopulation' or population of populations (eg Wade and Goodnight, 1998). The large number of subpopulations in a metapopulation allows the large absolute numbers of individuals needed to generate the necessary mutations, whereas the small size of the individual subpopulations allow for drift to dominate over selection. However, this metapopulation model is itself controversial (Coyne *et al*, 1997).

In a new development, Weinreich and Chao (2005) point out that although we may consider a large population 'fixed' for the ab genotype, in fact it will be in mutation selection balance. In a population initially fixed for the ab genotype, there will be mutations resulting in the Ab genotype and the aB genotype. We can model these as pure deleterious mutations since double mutations to AB are rare enough to be considered non-existent. Thus, under standard mutation-selection balance modified for the haploid system modeled by Weinreich and Chao, the expected frequency of the

Ab genotype is $\hat{q}_A \approx \mu_A/S_A$, where \hat{q}_A is the equilibrium frequency of the A allele, μ_A is the mutation rate to the A allele, and S_A is the selection against Ab genotypes relative to ab genotypes. There will be a similar equation for the frequency of the aB genotype. The important point is that in a large population there will be a substantial population of the transient genotypes, and the larger the population the greater the number of transient genotypes that will be present. For example, chemostat experiments with *Escherichia coli* typically maintain a population size of 10^6 to 10^9 cells per milliliter (Hartl and Clark, 1997). If the mutation rate is 10^{-5} , and selection against the Ab genotype relative to the ab genotype is 0.25 (to pick a number out of a hat), then we would expect between 40 and 40 000 Ab genotypes per milliliter. Members of this population of transient genotypes enter through mutation, and are eventually eliminated by selection. Even though these genotypes are always in flux they remain a population that are subject to mutation at the B locus. When you add the potential for mutations at the B locus, the pool of transient (Ab and aB) genotypes effectively doubles. As a result, in large populations, it simply becomes a matter of waiting for a mutation to occur in this standing population of transient genotypes to occur. Furthermore, the larger the population size the shorter will be the waiting time.

This mechanism differs markedly from previously proposed mechanisms for peak shifts. Unlike previous models, because this model is based on stochastic events in very large populations, the transition from lower to higher peaks becomes a virtual certainty in very large populations. It is, of course, still a stochastic event; however, it now becomes a question of the expected waiting time, not whether or not the peak shift will occur.

That said, there are some severe limitations of this model. Most importantly the A and B loci must be tightly linked. In the example above, the transient genotypes are only 1/25 000th of the population. Recombination will break up any new mutations to the favorable genotype since recombination will nearly always involve an ab genotype (although the authors point out that a very small amount of recombination can be favorable). In addition, the model examines a haploid genetic system. The assumptions of low recombination and haploidy are appropriate for

bacterial systems, but there is more interest in the diploid genetics that typifies higher organisms. The basic ideas put forth in this model are certainly interesting; it will be equally interesting to see if the model holds up when there is diploidy and the increased recombination typical of sexual organisms.

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