The Burden of Genetic Load

Fifty Years of Genetic Load. An Odyssey. BRUCE WALLACE. Cornell University Press, Ithaca, NY, 1991. xiv, 174 pp., illus. $31.50.

It seemed like a simple experiment: irradiate a population of *Drosophila* and use the decrease in the average fitness of the population to learn more about the detrimental effects of mutations. You can imagine Bruce Wallace's surprise when the fitness of the irradiated population turned out to be higher than that of the control population. Paradoxes make science exciting; this one has excited Wallace for more than 40 years.

The original motivation for the experiment was as a test of genetic load theory. The average fitness of a population is depressed by deleterious alleles held in the population by the balance between mutation and natural selection. The depression is called the genetic load of the population. Surprisingly, the load does not depend on the magnitude of the deleterious effect of alleles, but only on the mutation rate. Mathematically, we could write $L = 2u$—the genetic load is equal to twice the mutation rate—as was first done by J. B. S. Haldane in 1937. Load theory makes a simple prediction: If we increase the mutation rate, we must increase the genetic load. If we increase the mutation rate experimentally and don't see an increase in the genetic load, we must reject some or all of Haldane's paradigm. In fact, Wallace showed that the load decreased, yet we (the community of population geneticists) clung to Haldane's paradigm. So much for the scientific method.

Wallace originally observed the increase in the average fitness of an irradiated population in the early 1950s. A variety of experiments by Wallace and others have shown the observation to be repeatable. However, it must be stressed that the increase is only seen when two conditions are met. The original (and control) populations must be homozygous and the number of mutations must be small. Otherwise, the decrease in fitness predicted by load theory will be observed.

A major weakness of the original design was its reliance on the average fitness of the population. Subsequent experiments have measured the average viabilities of individual chromosomes using balanced-lethal systems. The most extensive experiments of this sort were performed by the late Terumi Mukai who showed (via a somewhat indirect argument) that the mean viability of a fly will increase with the number of spontaneous mutations to a maximum at about 12 mutations and will steadily decrease as the number of mutations increases beyond this. His experiments are, for me, the cleanest demonstration of what I would love to call "the Wallace effect," were this phrase not already used in the allopatric speciation model.

No progress has been made in our understanding of the mechanism for the increase in viability. Wallace does make a few suggestions. However, in this era of reductionism, it is hard to take molecular models seriously without direct experimental verification. In principle, we could learn the molecular basis of the Wallace effect. In fact, the effect is so weak that the designs may be impractical.

But our real interest must rest not with the Wallace effect itself, but rather with Wallace's attempts to reconcile the effect with Haldane's load paradigm. Much of Wallace's scientific work over the past 40-odd years has been centered on precisely this problem. His answer has been to inject ecology into his population genetic models and seek a resolution in explicit use of terms reflecting the regulation of population size. Though it is not clear how his ecologically aware models can explain the Wallace effect, it is clear that they provide a ready answer to load theory's more significant role in population genetics. Recall that Motoo Kimura used load theory to argue that most molecular variation is neutral. His view was (and is) that the high levels of variation seen at the molecular level could not be responding to natural selection without incurring an overwhelming genetic load. Wallace's response is that Haldane's paradigm is inadequate and that with a little demography we can eliminate most of the load while retaining the rates of evolution.

Fifty Years of Genetic Load is Wallace's recounting of his involvement in these issues. It is a delightful book to read, as it mixes science with personal anecdotes and insights from someone who portrays himself as a gadfly. It is risky to write a book summing up one's personal assessment of one's contributions to science. Yet Wallace seems to have a healthy understanding of his positioning somewhat aside from the mainstream of population genetics. If the book has a weakness, it is in its inadequate coverage of the contributions of others to load theory. There is no mention of the contributions of Warren Ewens discrediting the assumption that the load should be measured relative to a genotype that would not exist even in the largest imaginable population. Joe Felsenstein's important load paper, which uses demographic arguments to soften load's impact, is missing as well. One could argue that load theory's gradual recession from the front lines of population genetics has been due primarily to the work of Bodmer, Milkman, Sved, King, Ewens, Reed, and Felsenstein, among others. Yet these players are hardly mentioned at all.

I think there is one aspect of this book that should be taken very seriously by population geneticists. Wallace spends most of the book wrestling with the concept of the mean fitness of a population. (The genetic load of a population is a linearly decreasing function of the mean fitness.) He doesn't seem to have come to grips with the concept after more than 40 years of effort, nor has anyone else. For me, the obvious conclusion is that population genetics theory has nothing of substance to say about the mean fitness of a population. Rather, the province of the theory should lie exclusively with dynamics. We can hope to describe the changes in the genetic composition of a population given information about the relative fitnesses of genotypes, mutation rates, and so on. We cannot hope to predict *through purely theoretical arguments* whether these changes will improve or depreciate the situation of the population. Given the extraordinary importance attached to the fundamental theorem of natural selection and the current spate of evolutionarily-stable–strategy arguments, this conclusion will be viewed as heretical. Yet, if Wallace's book is telling us anything, it is that something is very wrong with population geneticists' obsession with the mean fitness of a population.

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