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Nei M, Maruyama T & Chakraborty R. The bottleneck effect and genetic variability in populations. *Evolution* 29:1-10, 1975.
[Center for Demographic and Population Genetics, University of Texas, Houston, TX]

A mathematical theory of the effects of population bottlenecks on genetic variability is developed. This work has provided a theoretical basis for studying protein polymorphism, speciation, and other evolutionary questions. [The *SCI*® indicates that this paper has been cited in over 205 publications.]

Bottlenecks, Polymorphism, and Speciation

Masatoshi Nei
Center for Demographic and
Population Genetics
University of Texas Health Science Center
Houston, TX 77225

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In the early 1970s, there was a great controversy over the mechanism of maintenance of protein polymorphism in natural populations.[1] Neutralists argued that a large proportion of protein polymorphism is selectively neutral or nearly neutral, whereas selectionists contended that it is maintained by some form of balancing selection. One of the patterns of protein polymorphism established by that time was that average heterozygosity (proportion of heterozygous loci per individual) does not necessarily increase with increasing population size as predicted from the neutral theory and that there is apparently an upper limit of average heterozygosity that is rather low (30 percent). Selectionists took this as evidence against the neutral theory. To resolve this problem, T. Ohta proposed that most mutations at the protein level are not really neutral but are slightly deleterious relative to a few well-adapted alleles.[2] This model was capable of explaining the upper limit of average heterozygosity but produced an undesirable prediction that amino-acid substitution in proteins is slowed down or virtually stops in large populations, which was contradictory with actual observations.

Another possible explanation for the upper limit of average heterozygosity was the idea that natural populations occasionally go through bottlenecks, since bottlenecks were known to reduce genetic variability drastically. However, there was no theoretical study on this problem, and it was not clear whether this was a sufficient explanation. At that time most biologists believed on intuitive grounds that genetic variability is reduced drastically under the bottleneck effect but recovers rather quickly, particularly in organisms with short generation time. One day in 1973, I discussed this problem with my colleague Ranajit Chakraborty and decided to study it mathematically, considering the bottleneck size, the rate of population growth after a bottleneck, and the rate of amino-acid substitution in proteins. This project was later joined by Takeo Maruyama, a visitor from Japan. (On December 11, 1987, Maruyama unexpectedly died of a heart attack at the age of 51.)

This study led to three new findings (predictions): (1) the amount of reduction in genetic variability under the bottleneck effect depends not only on the bottleneck size but also on the rate of population growth; (2) once heterozygosity is reduced, it takes hundreds of thousands of years for it to recover to the original level; (3) the number of alleles per locus is reduced more drastically than is average heterozygosity. The second finding was significant in showing that the bottleneck effect can indeed be the factor causing the upper limit of average heterozygosity. Our later study showed that most data on protein polymorphism can be explained by the neutral theory if the bottleneck effect is taken into account.[3]

However, this is not the only reason this paper was cited so much immediately after publication. Many authors cited it because it provided a theoretical basis for studying speciation, the biology of colonizing species, and the fate of endangered species. Some authors provided empirical support for our theory—examining the cases where population bottlenecks are known to have occurred in recent history.

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1. **Kimura M.** *The neutral theory of molecular evolution.* Cambridge, England: Cambridge University Press, 1983. 367 p. (Cited 300 times.)
2. **Ohta T.** Slightly deleterious mutant substitutions in evolution. *Nature* 246:96-8, 1973. (Cited 50 times.)
3. **Nei M & Graur D.** Extent of protein polymorphism and the neutral mutation theory. *Evol. Biol.* 17:73-118, 1984. (Cited 25 times.)

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