THE NEO-DARWINIAN THEORY AND
THE NEUTRAL MUTATION HYPOTHESIS

Darwin proposed his theory of evolution by natural selection without knowledge of the sources of variation in populations. After Mendel's laws were rediscovered and genetic variation was shown to be generated by mutation, Darwinism and Mendelism were used as the framework of what came to be called the synthetic theory of evolution, or neo-Darwinism. According to this theory, mutation is recognized as the ultimate source of genetic variation, but natural selection is given the dominant or "creative" role in shaping the genetic makeup of populations and in the process of gene substitution.

In time, neo-Darwinism became a dogma in evolutionary biology, and selection came to be considered the only force capable of driving the evolutionary process, while other factors such as mutation and random drift were thought of as minor contributors at best. This particular brand of neo-Darwinism was called selectionism.

According to the selectionist or neo-Darwinian perception of the evolutionary process, gene substitutions occur as a consequence of selection for advantageous mutations. Polymorphism, on the other hand, is maintained by balancing selection. Thus, neo-Darwinists regard substitution and polymorphism as two separate phenomena driven by different evolutionary forces. Gene substitution is the end result of a positive adaptive process, whereby a new allele takes over future generations of the population if and only if it improves the fitness of the organism, while polymorphism is maintained when the coexistence of two or more alleles at a locus is advantageous for the organism or the population. Neo-Darwinian theories maintain that most genetic polymorphisms in nature are stable.

The 1960s witnessed a revolution in population genetics. The introduction of electrophoresis into population genetics studies soon led to the discovery of the existence of large amounts of genetic variability in natural populations such as human and Drosophila populations (Harris 1966; Lewontin and Hubby 1966). The availability of protein sequence data removed the species boundary in population genetics studies and for the first time provided adequate empirical data for examining theories pertaining to the process of gene substitution. In 1968, Kimura postulated that the majority of molecular changes in evolution are due to the random fixation of neutral or nearly neutral mutations (Kimura 1968a); it was also independently proposed by King and Jukes (1969). This hypothesis, now known as the neutral theory of molecular evolution, contends that at the molecular level the majority of evolutionary changes and much of the variability within species are caused neither by positive selection of advantageous alleles nor by balancing selection, but by random genetic drift of mutant alleles that are selectively neutral or nearly so. Neutrality, in the sense of the theory, does not imply strict equality in fitness for all alleles. It only means that the fate of alleles is determined largely by random genetic drift. In other words, selection may operate, but its intensity is too weak to offset the influences of chance effects. For this to be true, the absolute value of the selective advantage or disadvantage of an allele must be smaller than $1/(2N_e)$.

According to the neutral theory, the frequency of alleles is determined largely by stochastic rules, and the picture that we obtain at any given time is merely a transient state representing a temporary frame from an ongoing dynamic process. Consequently, polymorphic loci consist of alleles that are either on their way to fixation or on their way to extinction. Viewed from this perspective, all molecular manifestations that are relevant to the evolutionary process should be regarded as the result of a continuous process of a mutational input and a concomitant random extinction or fixation of alleles. Thus, the neutral theory regards substitution...
and polymorphism as two facets of the same phenomenon. Substitution is a long and gradual process, whereby the frequencies of mutant alleles increase or decrease randomly, until the alleles are ultimately fixed or lost by chance. At any given time, some loci will possess alleles at frequencies that are neither 0% nor 100%. These are the polymorphic loci. According to the neutral theory, most genetic polymorphism in populations is transient in nature.

The essence of the dispute between neutralists and selectionists essentially concerns the distribution of fitness values of mutant alleles. Both schools agree that most new mutations in proteins are deleterious and that these mutations are quickly removed from the population so that they contribute neither to the rate of substitution nor to the amount of polymorphism within populations. The difference concerns the relative proportion of neutral mutations among nondeleterious mutations. While selectionists maintain that very few mutations are selectively neutral, neutralists maintain that most nondeleterious mutations are effectively neutral. Of course, not all selectionists hold the same view of evolution nor do all neutralists (see reviews by Lewontin 1974; Kimura 1983; Nei 1987; Gillespie 1991). For example, Ohta’s (1973, 1974) hypothesis of slightly deleterious mutation emphasizes the importance of slightly deleterious mutations in gene substitution and molecular polymorphism, whereas in Nei’s (1987) view such mutations do not play an important role.

The heated controversy over the neutral-mutation hypothesis during the last two decades has had a strong impact on molecular evolution. First, it has led to the general recognition that the effect of random drift cannot be neglected when considering the evolutionary dynamics of molecular changes. Second, the synthesis between molecular biology and population genetics has been greatly strengthened by the introduction of the concept that molecular evolution and genetic polymorphism are but two facets of the same phenomenon (Kimura and Ohta 1971a). Although the controversy still continues, it is now recognized that any adequate theory of evolution must be consistent with both of these aspects of the evolutionary process at the molecular level.