**Course: Advanced Bioinformatics**

**Module title: Neutral theory**

**Module no. : 52**

**Neutral theory of molecular evolution**

The neutral theory of molecular evolution holds that at the molecular level most evolutionary changes and most of the variation within and between species is not caused by natural selection but by random drift of mutant alleles that are neutral. A neutral mutation is one that does not affect an organism's ability to survive and reproduce. The neutral theory allows for the possibility that most mutations are deleterious, but holds that because these are rapidly purged by natural selection, they do not make significant contributions to variation within and between species at the molecular level. Mutations that are not deleterious are assumed to be mostly neutral rather than beneficial. In addition to assuming the primacy of neutral mutations, the theory also assumes that the fate of neutral mutations is determined by the sampling processes described by specific models of random genetic drift.

**Overview**

Kimura, King, and Jukes suggested that when one compares the genomes of existing species, the vast majority of molecular differences are selectively "neutral", i.e. the molecular changes represented by these differences do not influence the fitness of organisms. As a result, the theory regards these genomic features as neither subject to, nor explicable by, natural selection. This view is based in part on the degenerate genetic code, in which sequences of three nucleotides (codons) may differ and yet encode the same amino acid (GCC and GCA both encode alanine, for example). Consequently, many potential single-nucleotide changes are in effect "silent" or "unexpressed" (see synonymous or silent substitution). Such changes are presumed to have little or no biological effect. However, it should be noted that the original theory was based on the constancy of the rates of amino acid substitutions and hypothesized that the majority of the substitutions were also neutral.

A second hypothesis of the neutral theory is that most evolutionary change is the result of genetic drift acting on neutral alleles, rather than for example genetic hitchhiking of a neutral allele due to genetic linkage with non-neutral alleles. After appearing by mutation, a neutral allele may become more common within the population via genetic drift. Usually, it will be lost, or in rare cases it may become fixed, meaning that the new allele becomes standard in the population. This stochastic process is assumed to obey equations describing random genetic drift by means of accidents of sampling.

According to the neutral theory, mutations appear at rate μ in each of the 2N copies of gene, and fix with probability 1/(2N). This means that if all mutations were neutral, the rate at which fixed differences accumulate between divergent populations is predicted to be equal to the per-individual mutation rate, e.g. during errors in DNA replication; both are equal to μ. When the proportion of mutations that are neutral is constant, so is the divergence rate between populations. This provides a rationale for the molecular clock, although the discovery of a molecular clock predated neutral theory.

Many molecular biologists and population geneticists also contributed to the development of the neutral theory, which is different from the neo-Darwinian theory.

Neutral theory does not deny the occurrence of natural selection. Hughes writes: "Evolutionary biologists typically distinguish two main types of natural selection: purifying selection, which acts to eliminate deleterious mutations; and positive (Darwinian) selection, which favors advantageous mutations. Positive selection can, in turn, be further subdivided into directional selection, which tends toward fixation of an advantageous allele, and balancing selection, which maintains a polymorphism. The neutral theory of molecular evolution predicts that purifying selection is ubiquitous, but that both forms of positive selection are rare, whereas not denying the importance of positive selection in the origin of adaptations.