E-content

M.Sc. Zoology (Semester II)
CC8- Biosystematics and Evolution

Unit: 3.4

Neutral theory of molecular evolution

Dr Gajendra Kumar Azad
Assistant Professor
Post Graduate Department of Zoology
Patna University, Patna
Email: gkazadpatnauniversity@gmail.com

Molecular evolution concerns how gene sequences change over time. The accumulation of changes in gene sequences constitutes evolution, which can lead to different characteristics and subsequently give rise to different species.

Change in DNA sequences is commonly brought on by mutations. Mutations can be inherited, but are also occurring during cell replication. When a mutation arises that is advantageous to the individual, certain advantages in life and reproduction may ensue.

Advantageous mutations, therefore, have a selective advantage, where they can be selected for and spread throughout the population.

Deleterious mutations, on the other hand, are more likely to be removed from the population.

Genetic drift and natural selection are the two most important cause of allele substitution or variations observed in the population. This phenomenon is also referred as polymorphism.

The Neutral Theory

Different ideas about the degree of polymorphism in real populations have been entertained at various times in the history of evolutionary theory.

During the early days of the modern synthesis, it was generally believed that natural selection very quickly removed any disadvantageous alleles, and that a single predominant allele (the so-called “wild-type”) was present at most loci.

Occasionally an advantageous mutation would arise, and it would then very quickly be brought to fixation, replacing the previous wild-type in the process. This viewpoint is now referred to as the “Classical School”.

In contrast to this view, the so-called “Balance School” believed that an appreciable amount of polymorphism was present in real populations. It was believed that polymorphism was being actively maintained by natural selection.

One way in which selection can maintain several alleles in a population of diploid organisms is if heterozygotes are more fit than homozygotes, but there are also other selection-based scenarios with this outcome.

According to both schools of thought, essentially all evolutionary change (meaning change in genotype frequencies) was brought about by natural selection.

At the time it was not possible to directly measure molecular diversity. When the first electrophoretic studies of protein polymorphism were published in the 1960's, the level of genetic diversity was much higher than anticipated by adherents of either school of thought.

The classic hypothesis was obviously wrong (as there was in fact a great deal of polymorphism at many loci), but even the balance theory did not seem to be able to account for the observed levels of polymorphism.

This led ***Motoo Kimura (1968)***, ***Jack King and Thomas Jukes (1969)*** to propose the 'neutral theory' of molecular evolution. According to 'neutral theory' of molecular evolution the majority of molecular changes, such as in DNA sequence, are caused by random processes acting on selectively neutral mutants, meaning they inferred no advantage or disadvantage.

According to "Neutral Theory" of molecular evolution most mutations are disadvantageous and are quickly removed by natural selection, a vanishingly small proportion are advantageous and are quickly brought to fixation, while the vast majority of fixed (and therefore observed) mutations are selectively neutral.

Kimura, compared the amino acid sequences of hemoglobin α and cytochrome *c* in several mammalian species and found that the number of mutant substitutions was too large to be tolerable within Haldane's theory of natural selection if the substitution number was extrapolated to the total genome. Based on this discrepancy, Kimura proposed the neutral theory.

In his paper (Kimura) explained various interesting observations that has been verified by independent researchers and also observed in recent studies such as:

1. Synonymous base substitutions (i.e., those that do not cause amino acid changes) occur almost always at a much higher rate than nonsynonymous substitutions.

2. Noncoding sequences, such as introns, evolve at a high rate similar to that of synonymous sites.

3. Pseudogenes, or dead genes, evolve at a high rate.

The neutral theory proposed by Kimura was based on most highly refined mathematical models in biology using complex calculations.

Mathematical demonstration of Neutral theory

The most important contribution of Kimura's work is that it provides a theoretical framework for developing methods that detect the action of selection within genomes.

However, to be able to demonstrate that a sequence is subject to selective pressure, one must reject the null hypothesis that this sequence evolves neutrally.

For example, one strong (and elegant) prediction of the neutral theory is that at selectively neutral sites, the rate of substitution is equal to the rate of mutation (Kimura, 1968).

To demonstrate this, consider a neutral site: a DNA position at which all alleles are selectively equivalent, and where the rate of mutation per generation is u.

In a haploid population of size N, Nu mutations occur at this site at each generation.

Given that there is no selection, all genotypes have the same probability to reach fixation. Under a neutral model, the probability that an allele or mutation fixes is simply its relative frequency in the population.

For a new mutation in a haploid population, this relative frequency is $1/N$; thus, the probability that a new mutation reaches fixation is simply $1/N$ (the same reasoning also holds for diploid species).

The rate of substitution per generation (K) is obtained simply by multiplying the number of mutations that occur at each generation by their probability of fixation.

Thus, for neutrally evolving sites, the equation becomes the following:

$$K = Nu \times 1/N = u$$

Of course, because of natural selection, advantageous mutations have a higher probability of fixation than neutral mutations, and deleterious mutations have a lower probability of fixation.

It therefore follows that sequences subject to positive selection evolve faster than neutral sites ($K > u$), whereas sequences subject to negative selection evolve more slowly ($K < u$). This simple result is the basis of many tests that have been developed to detect selection.

By mathematical calculations Kimura showed that the rate of evolution cannot be explained by positive or negative selection because it is too high and that many mutations must instead be neutral.

Neutral mutations become widespread by a process called random genetic drift, in which a mutation spreads throughout the population due to chance alone.

That most mutations are disadvantageous and rarely observed is in agreement with the previously prevalent views (now referred to as “selectionist”).

Selectionists and neutralists also agree that adaptation must be the result of advantageous mutations that are brought to fixation by natural selection.

The main point of difference concerns the fraction of mutations that are advantageous: the extreme selectionist view is that almost all observed mutations are advantageous, while the neutralist believes that practically all observed mutations are neutral with respect to fitness.

Today, we have many examples of mutations that appear to have been fixed by natural selection, but there is also a great deal of evidence for the importance of neutral mutation and genetic drift. The truth probably lies somewhere between the two extreme viewpoints.

Validation of neutral theory

The neutral theory provided a much-desired null hypothesis to test empirical genetic data against. To show that a sequence is being selected upon, one needs to be able to reject the null hypothesis that the sequence is evolving neutrally.

The neutral theory has been used as a basis for many statistical tests which investigate genetic variance.

DNA sequence data grew in use during the late 20th century, and many of the discoveries from these sequencing experiments supported the predictions of the neutral theory.

For example, it was found that changes in protein sequences were more likely to be conservative (*i.e.* less likely to affect protein function) than radical, and that pseudogenes ("dead" genes which do not have a function) evolve at a high rate.

Both of these findings were seen as support for the idea that divergence between species is due to neutral evolution in less functionally important regions. In other words, if most mutations were adaptive, more changes in important genetic regions than would be expected.

References

(2008), *Nature Education* 1(1):218

Evolution by Douglas J. Futuyma

Integrated Molecular Evolution by Scott Orland Rogers

---------- End ----------