Revision Module

Neutral Theory of Molecular Evolution

Neutral Theory of Molecular Evolution (Kimura)

- Proposed by Motoo Kimura (1968).
- States that most molecular-level evolutionary changes are caused not by natural selection but by random fixation of neutral mutations.
- Neutral mutations do not affect survival or reproduction, so natural selection neither favors nor removes them.

Thus, genetic drift, not selection, is the major force at the molecular level.

2. Major Assumptions of Neutral Theory

1. Most mutations are neutral in their effects on fitness.

2. Population size is finite, so drift can operate.

3. Neutral mutations appear at a steady rate (mutational input is constant).

4. Fixation of neutral mutations is random, guided by genetic drift.

5. Rate of molecular evolution equals the neutral mutation rate (because if a neutral mutation appears at rate μ, and its fixation probability is $1/2N$, total rate $= \mu \times 2N \times (1/2N) = \mu$).

3. Evidence Supporting Neutral Theory

- High genetic variation observed in natural populations cannot be fully explained by selection alone.
- Molecular clock: many genes evolve at nearly constant rates across lineages.
- Higher substitution rates in non-functional DNA (pseudogenes, introns) where selection is absent.

- Synonymous (silent) changes > Non-synonymous (amino acid) changes, showing most mutations do not affect protein function.

4. Neutral Mutations

What are neutral mutations?:

- Mutations that do not affect phenotype or fitness.
- No advantage, no disadvantage.
- Invisible to natural selection.

How do they appear?

Neutral mutations originate from:

- Errors during DNA replication
- Spontaneous chemical changes (deamination, oxidation)
- Environmental mutagens (radiation, chemicals)
- Repair errors

Because they do not affect survival, they stay in the population only by chance.

5. Genetic Drift

- Random change in allele frequencies across generations.
- Stronger in small populations, weaker in large ones.
- Can lead to fixation or loss of alleles regardless of their effects.
- Drift is the engine that drives the fixation of neutral mutations.

Examples: founder effect, bottleneck effect.

6. Substitution Rate

Mutation = new change in DNA.

Substitution = when that mutation spreads through the population and becomes the new normal allele.

Substitution rate = the rate at which new mutations become fixed in a population.

Kimura showed that for neutral mutations, the substitution rate does not depend on population size, and equals the neutral mutation rate (μ).

7. Synonymous and Non-Synonymous Mutations

Synonymous mutations:

- Also called silent mutations.
- Do not change the amino acid in the protein (due to redundancy of genetic code).
- Usually neutral because the protein remains unchanged.
- Example: GAA → GAG (both code for glutamic acid).

Non-synonymous mutations

- Change the amino acid sequence of the protein.
- Can be: Deleterious (most common), Neutral (if change does not affect protein function), Advantageous (rare)

Because selection acts against harmful changes, the number of nonsynonymous mutations that get fixed is usually much lower.

Why this matters for Neutral Theory:

High rate of synonymous substitutions vs. low rate of nonsynonymous substitutions is strong evidence that most evolution at the molecular level is neutral.

8. Rate of Molecular Evolution = Neutral Mutation Rate

According to Kimura, if neutral mutations arise at rate μ, the rate at which they become fixed in the population is also μ.

Population size cancels out mathematically.

This is a key prediction and supports the molecular clock.

9. Molecular Clock

1. DNA and proteins evolve at roughly constant rates over time.

2. This happens because neutral mutations accumulate steadily.

3. Therefore, the amount of sequence difference reflects time since divergence.

4. If substitution rate is known, evolutionary time can be estimated. Example: Human–chimp DNA difference implies a split ~6–7 million years ago.