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Fifty years of Neutral Theory

Genomics, Bioinformatics & Evolutionary Biology
Dept Genetics and Microbiology,
University Autonoma of Barcelona Barcelona, Spain
Evolutionary Rate at the Molecular Level

by

MOTOO KIMURA
National Institute of Genetics,
Mishima, Japan

Calculating the rate of evolution in terms of nucleotide substitutions seems to give a value so high that many of the mutations involved must be neutral ones.

Comparative studies of haemoglobin molecules among different groups of animals suggest that, during the evolutionary history of mammals, amino-acid substitution has taken place roughly at the rate of one amino-acid change in $10^7$ yr for a chain consisting of some 140 amino-acids. For example, by comparing the $\alpha$ and $\beta$ chains of man with those of horse, pig, cattle and rabbit, the figure of one amino-acid change in $7 \times 10^4$ yr was obtained.

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This is roughly equivalent to the rate of one amino-acid substitution in $10^7$ yr for a chain consisting of 100 amino-acids.

A comparable value has been derived from the study of the haemoglobin of primates. The rate of amino-acid substitution calculated by comparing mammalian and avian cytochrome $c$ (consisting of about 100 amino-acids) turned out to be one replacement in $45 \times 10^4$ yr (ref. 3).

Also by comparing the amino-acid composition of human triosephosphate dehydrogenase with that of rabbit and

\[ K = \mu_0 \]
Fifty years of Neutral Theory

K = \mu_0
Motoo Kimura

1944 Kioto Imperial University (Major Citology - Dpt Botany, Fac Sciences)

1949 National Institute of Genetics in Mishima
Paper S. Wright 1931’s paper “Evolution en Mendelian populations”

1953 United States to study on a Fulbright Fellowship. James Crow's laboratory at the University of Wisconsin

1955 Kimura paper and talk Cold Spring Harbor Symposium diffusion theory applied to allele freq

1956 Ph.D. dissertation. Return to Japan

1968. Nature’s paper

Born 1924 November 13, Okazaki, Japan
Died 1994 November 13 Shizuoka, Japan

\[ K = \mu_0 \]
Evolution is the process of conversion of individual variation into species variation.
Evolution is the process of conversion of individual variation into species variation

Divergence
Species level

Polymorphism
Population level

Mutation
Individual level

Population genetics: the kinematics and dynamics of evolutionary changes

Evolutionary forces
- Mutation
- Genetic drift
- Genetic flux
- Natural selection
- Recombination

\[ K = \mu_0 \]
Evolution is the process of conversion of individual variation into species variation.

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Individual level

K = \mu_0
How does allelic frequency change over time?

Population genetics: the kinematics and dynamics of evolutionary changes in populations

$K = \mu_0$
$K = \mu_0$
\( K = \mu_0 \)

Probability of fixation of new mutations in populations

\[ u(N_e, s) \approx \frac{1 - \exp[-2cN_es]}{1 - \exp[-2cN_es]} \]

\[ \tilde{t}_{fix} = 4N \text{ gen.} \]

\[ \tilde{t}_{lost} = 2 \ln N \]

Motoo Kimura (1957)
Molecular clock in divergent amino acid sequences (1965)

First measures of genetic variation in natural populations by gel electrophoresis (1966)

A molecular approach to the study of genic heterozygosity in natural populations. II. Amount of variation and degree of heterozygosity in natural populations of Drosophila pseudoobscura

R. C. Lewontin and J. L. Hubby
Department of Zoology, University of Chicago, Chicago, Illinois
Received March 30, 1966


R. C. Lewontin

$K = \mu_0$
Calculating the rate of evolution in terms of nucleotide substitutions seems to give a value so high that many of the mutations involved must be neutral ones.
Panselecccionism

\[ K = \mu_0 \]
Evolution is the process of conversion of individual variation into species variation

- **Divergence**
  - Species level

- **Polymorphism**
  - Population level

- **Mutation**
  - Individual level

**Population genetics:** the kinematics and dynamics of evolutionary changes

- Mutation
- Genetic drift
- Genetic flux
- Natural selection
- Recombination

\[ K = \mu_0 \]
Non-Darwinian Evolution

Most evolutionary change in proteins may be due to neutral mutations and genetic drift.

Jack Lester King and Thomas H. Jukes

Darwinism is so well established that it is difficult to think of evolution except in terms of selection for desirable characteristics and advantageous genes. New technical developments and new knowledge, such as the sequential analysis of proteins and the deciphering of the genetic code, have made a much closer examination of evolutionary processes possible, and therefore necessary. Patterns of evolutionary change that have been observed at the phenotypic level do not necessarily apply at the genotypic and molecular levels. We need new rules in order to understand the patterns and dynamics of molecular evolution.

Evolutionary change at the morphological, functional, and behavioral levels results from the process of natural selection, operating through adaptive changes in DNA. It does not necessarily follow that all, or most, evolutionary change in DNA is due to the action of Darwinian natural selection. There appears to be considerable latitude at the molecular level for random genetic changes that have no effect upon the fitness of the organism. Selectively neutral mutations, if they occur, become passively fixed as evolutionary changes through the action of random genetic drift.

The idea of selectively neutral change at the molecular level has not been readily accepted by many classical evolutionists, perhaps because of the pervasiveness of Darwinian thought. Change in DNA and protein, when it is thought of at all, is thought to be limited to a response to activities at a higher level. For example, Simpson (1) quotes Weiss (2) as stating that there is a cellular control of molecular activities, and Simpson adds that there is also an organismal control of cellular activities and a populational control of organismal activities, and concludes (1):

The consensus is that completely neutral genes or alleles must be very rare if they exist at all. To an evolutionary biologist, it therefore seems highly improbable that proteins, supposedly fully determined by genes, should have nonfunctional parts, that dormant genes should exist over periods of generations, or that molecules should change in a regular but nonadaptive way... [natural selection] is the composer of the genetic message, and DNA, RNA, enzymes, and other molecules in the system are successively its messengers.

We cannot agree with Simpson that DNA is a passive carrier of the evolutionary message. Evolutionary change is not imposed upon DNA from without; it arises from within. Natural selection is the editor, rather than the composer, of the genetic message. One thing the editor does not do is to remove changes which it is unable to perceive.

The view that mutations cannot be selectively neutral is not confined to organismal evolutionists. Smith (3) states:

One of the objectives of protein chemistry is to have a full and comprehensive understanding of all the possible roles that the 20 amino acids can play in function and conformation. Each of these amino acids must have a unique survival value in the phenotype of the organism—the phenotype being manifested in the structures of the proteins. This is as true for a single protein as for the whole organism.

The "neutralist–selectionist" controversy

$K = \mu_0$
The neutral theory of molecular evolution

Motoo Kimura

1983
The neutral paradigm
Nothing in Biology Makes Sense Except in the Light of Evolution

Theodosious Dobzhansky

Nothing in Evolution Makes Sense Except in the Light of Population Genetics

Michael Lynch

Nothing in Population Genetics Makes Sense Except in the Light of Neutral Theory

Olga Dolgova

$K = \mu_0$
Distinctive features of Neutral Theory

- Simplicity
- Intelligibility
- Robustness
- Testable theoretical predictions
- Role chance in evolution
- Facilitator of adaptation
Distinctive features of Neutral Theory

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The general equation of molecular evolution

\[ K_i = \text{Prob fixation new mutant } i \]

\[ K_i = u(N_e, s) f(s) \, ds \]

Distribution of Fitness Effects

Probability of fixation
The general equation of molecular evolution

\[ K = 2N \mu \int_{-\infty}^{\infty} u(N_e, s) f(s) \, ds \]

Distribution of Fitness Effects

Probability of fixation

New mutations per site per generation
Neutral Theory of Molecular Evolution (1968)

**Assumption**

*New mutations are mainly neutral or strongly deleterious*

\[ K = \mu_0 \]

DFE (Distribution fitness effect of new mutation) of Kimura’s Neutral Theory
Neutral Theory of Molecular Evolution (1968)

**Assumption**

New mutations are mainly *neutral* or *strongly deleterious*
\[ K = \frac{1}{2N} \times \frac{1}{2N \mu_0} \]

New mutations entering each generation in the population

Probability of fixation

substitution / generation = (substitution / mutation) (mutation / generation)

Antonio Barbadilla
Theorem

K = µ₀

Substitution rate
or
Fixation rate
or
Evolutionary rate

= neutral mutation rate
\[ K = \mu_0 \]

Neutral mutation rate

\[ \mu_0 \]

Evolutionary rate

\[ K \]
$K = \mu_0$
Molecular Clock

Émile Zuckerkandl and Linus Pauling (1965)

• Divergence increases linearly over generation time

\[ K = \mu_0 \rightarrow D = 2T\mu_0 \]
Evolution is the process of conversion of individual variation into species variation

\[ K = \mu_0 \]
Most famous equations of Science

\[ E = mc^2 \]  
(Einstein’s relativity mass-energy equivalence)

\[ E\psi = \hat{H}\psi \]  
(Schrödinger general quantum wavefunction)

\[ S = k \log W \]  
(Boltzmann's entropy formula)

\[ F = ma \]  
(Newton’s dynamics 2nd law)

\[ K = \mu_0 \]  
(Kimura’s Neutral Evolutionary rate)
Neutral Theory of Molecular Evolution (1968)

\[ K = \mu_0 \]

Motoo Kimura

A minimalist theory
Distinctive features of Neutral Theory

- Simplicity
- Intelligibility
- Robustness
- Testable theoretical predictions
- Chance in evolution
- Facilitator of adaptation

K = µ
Intelligibility (descend with modification made clear)

Evolution is the process of conversion of individual variation into species variation

Divergence
Species level

Polymorphism
Population level

Mutation
Individual level

$\bar{K} = \mu_0$
Intelligibility (descend with modification made clear)

Evolution is the process of conversion of individual variation into species variation.

Selectionist view before Neutral theory

- Polymorphism (overdominance) Dobzhansky’s view.
- Divergence (positive Darwinian selection)

\[ K = \mu_0 \]
Intelligibility (descend with modification made clear)

Polymorphism within species as a transient phase of molecular evolution
Intelligibility (descend with modification made clear)

Selectionist view
- Polymorphism (overdominance)
- Divergence (positive Darwinian selection)

Neutral view
Polymorphism as a transient phase of molecular evolution

$K = \mu_0$
Polymorphism as a transient phase of molecular evolution

Divergence
Species level

Polymorphism
Population level

Mutation
Individual level

\( K = \mu_0 \)

Molecular Evolution

Population Genetics

\( T \rightarrow G \)
\( C \rightarrow C \)
Two main contributions of the Origin

1. The fact of the evolution of life: Descend with modification

2. Adaptations result from natural selection
Population dynamics of neutral and adaptive mutations

\[ K = \mu_0 \]

Allelic frequency

Time

Descend with modification

Adaptation
Neutral theory inspired coalescent theory: The genealogy of genes

Sir John Kingman - born at 1939


Neutral theory inspired coalescent theory

Pasado

Presente

$K = \mu_0$


Distinctive features of Neutral Theory

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The nearly-neutral theory

Ohta’s extension to Kimura’s neutral theory

Mutations are mainly neutral or slightly deleterious or strongly deleterious

\[ K = \mu_0 \]

The nearly-neutral theory

Effective selection $\rightarrow Ns$

Interplay $N$ and $s$

i. $|Ns| \leq 1$ effectively neutral realm

ii. $10 \leq |Ns| \geq 1$ nearly neutral

iii. $|Ns| \geq 10$ strong selection

- Generation time effect on $K$ ($K = \mu_0$)
- Frequency spectrum
- Codon bias
- Compensatory mutations
Distinctive features of Neutral Theory

• Simplicity
• Intelligibility
• Robustness
• Testable theoretical predictions
• Chance in evolution
• Facilitator of adaptation
DNA variation patterns (natural populations, somatic cell populations, phylomedicine, cultural evolution, conservation genetics...)

Constraint and variation

\[ \mu_0 = (1-f) \mu \]

Divergence

\[ K = \mu_0 \]

Polymorphism: nucleotide diversity (\( \pi \))

\[ \pi = \Theta = 4N \mu_0 \]

Derived allele frequency spectrum

\[ x(i) = \Theta \frac{1}{i} \]

Neutral, nearly-neutral and selective domains

\[ |N_e s| \]
The neutral paradigm play the role of universal null hypothesis
Methods for the detection of selection at the DNA level: searching for the footprint of natural selection on the pattern of genetic variation
**H₀**: Neutral prediction  
**H₁**: Rejection neutral prediction

### Types of selection/neutral tests

- Selection tests based on the allele frequency spectrum and/or levels of variability
- Selection tests based on comparisons of polymorphism and/or divergence between different classes of mutation
- Estimators derived from extensions of the McDonald and Kreitman test or the DFE
- Selection tests based on linkage disequilibrium (LD)
- Population differentiation and associated selection tests
The neutral paradigm play the role of universal null hypothesis

Falsifiability criterion

Sir Karl Popper
Distinctive features of Neutral Theory

- Simplicity
- Intelligibility
- Robustness
- Testable theoretical predictions
- Role chance in evolution
- Facilitator of adaptation
The Modern Synthesis

$K = \mu_0$
Role of chance in evolution

Mutation and Selection

Survival of the fittest
Role of chance in evolution

Mutation and Selection

2nd factor of chance

Genetic drift:
Random sampling of genes in finite populations

Survival of the fittest
Survival of the luckiest

1970
Distinctive features of Neutral Theory

- Simplicity
- Intelligibility
- Robustness
- Testable theoretical predictions
- Chance in evolution
- Facilitator of adaptation
Neutral variation as facilitator of adaptation by liberation of selective constraints

- Latent potential for selection (Dykhuizen-Hartl effect)
- Drift barrier theory (Genome complexity, M. Lynch 2007)
- Neutral gene networks (Robustness and Evolvability, A. Wagner 2008)


Challenges to Neutral Theory?
Neutral Theory of Molecular Evolution (1968)

Assumption

New mutations are mainly neutral or strongly deleterious

DFE (Distribution fitness effect of new mutation) of Kimura’s Neutral Theory
Population Dynamics of new mutations according the neutral paradigm

Selective variants do not contribute much to the polymorphism because of their ephemeral life at this stage.

\[ K = \mu_0 \]
Maps of Genome Selection in the *D. melanogaster*

Pervasive - Rampant – Ubiquitous

Around 30-50% of divergent amino acids are driven to fixation by positive selection

The hitch-hiking hypothesis
(recurrent linked selection)
Recurrent Linked Selection: the big challenge to the Neutral paradigm
On the 50th anniversary of the neutral theory of molecular evolution, we have been charged with the task of asking: how has the neutral theory fared in light of adaptive variation within and between species? In a word, poorly.

La estructura de los conceptos y las teorías científicas funcionan como redes conceptuales
Sobre la pesca

Somos como pescadores y nuestras teorías son como redes... Pero continuamente inventamos y tejemos redes nuevas y distintas y las lanzamos al agua, para ver lo que pescamos con ellas. No despreciamos ninguna red y en ninguna confiamos excesivamente, aunque preferimos cargar el barco con las redes más eficaces y dejar en el puerto las de menos uso.

Cap. 11 Sobre teorías físicas y teorías matemáticas

Fields of research where neutral theory is actively applied

- Population genetics (description and explanation of DNA variation patterns, including population genomics, paleogenomics and archeogenomics)
- Molecular evolution and phylogenetics
- Functional genomics
- Phenotypic evolution
- Transposable elements and evolution complex genome architecture
- Somatic cell populations (cancer cell, cell growth)
- Phylomedicine
- Human sociocultural phenomena
- Conservation genetics
- Microbial populations, rapidly evolving viral pathogens such as HIV
What is Neutral Theory?

\[ K = \mu \quad \text{and} \quad E = mc^2 \]
What is Neutral Theory?

- One of the most beautiful and elegant theories of science
- An extraordinary achievement of the human intellect
- A privileged conceptual perspective to understand how chance (mutation and genetic drift) and necessity (natural selection) account for biological evolution and adaptation
Deep down at the level of the genetic material, an enormous amount of evolutionary change has occurred, and is still occurring... The majority of such changes are not caused by natural selection but by random fixation of selectively neutral or nearly neutral mutants. This adds still more to the grandeur of our view of biological evolution.
En la profundidad del material genético, se ha producido y se sigue produciendo una enorme cantidad de cambios evolutivos... La mayoría de estos cambios no se deben a la selección natural sino a la fijación aleatoria de mutantes selectivamente neutros o casi neutros. Esto añade todavía más grandeza a nuestra visión de la evolución biológica.
Tomoko Ohta
July 2018