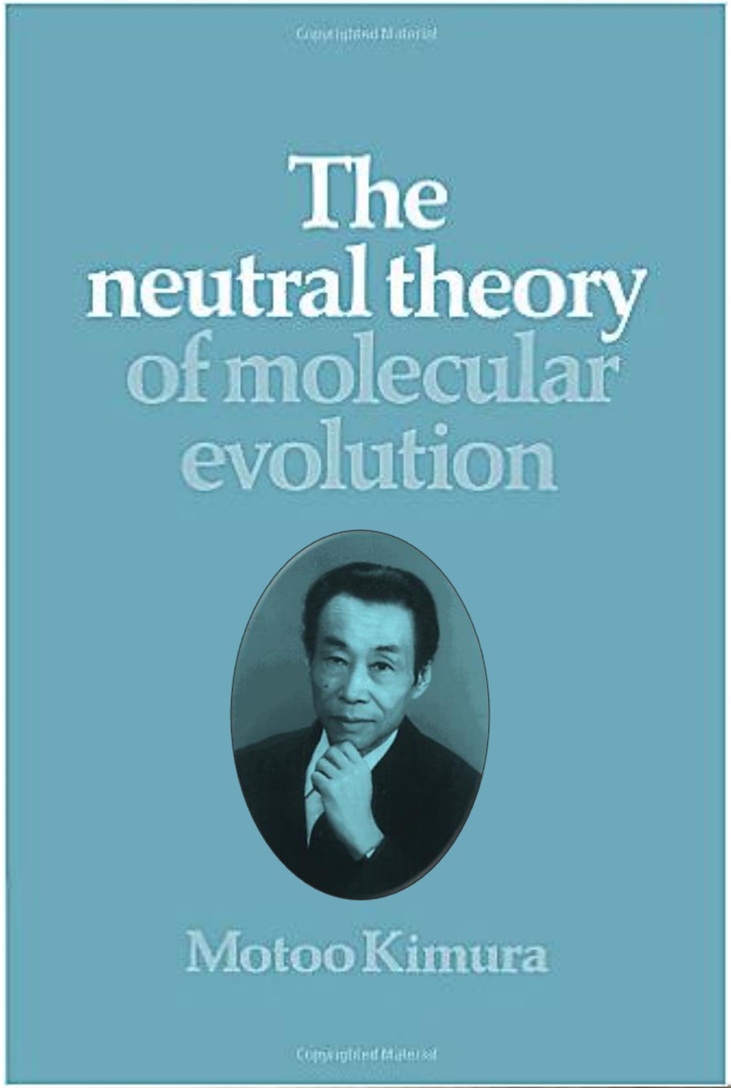

1968-2018 Fifty years of Neutral Theory

Genomics, Bioinformatics & Evolutionary Biology
Dept Genetics and Microbiology,
University Autonoma of Barcelona Barcelona, Spain

1968

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 α and β chains of man with those of horse, pig, cattle and rabbit, the figure of one amino-acid change in 7×10^6 yr was obtained[1].

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NATURE, VOL. 217, FEBRUARY 17, 1968 625

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[2]. 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 45×10^6 yr (ref. 3). Also by comparing the amino-acid composition of human triosephosphate dehydrogenase with that of rabbit and

substitution is

$$L(p) = 2\left\{\frac{1}{u(p)} - 1\right\} \int_0^{4Sp} \frac{e^y - 1}{y} dy - 2e^{-4S} \int_{4Sp}^{4S} \frac{e^y}{y} dy + 2 \log_e \left(\frac{1}{p}\right) \quad (1)$$

$K = \mu_0$

Smbe
Society for Molecular Biology & Evolution

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

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

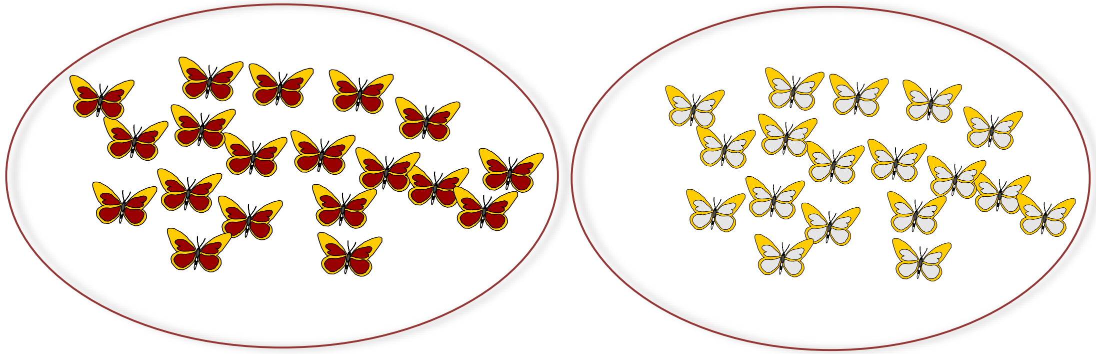
1968. Nature's paper

$K = \mu_0$

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

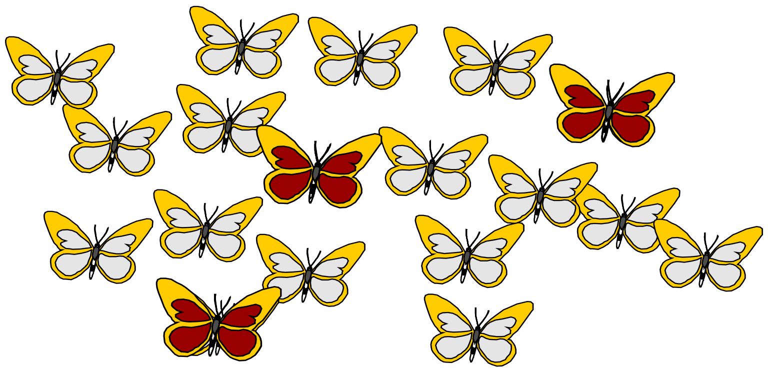
Evolution is the process of conversion of individual variation into species variation

Divergence
Species level



Population genetics:
the kinematics and dynamics of evolutionary changes

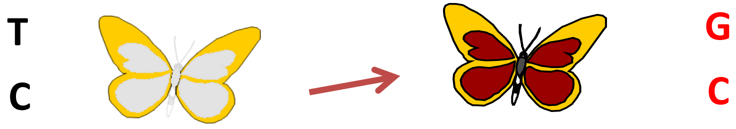
Polymorphism
Population level



Evolutionary forces

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

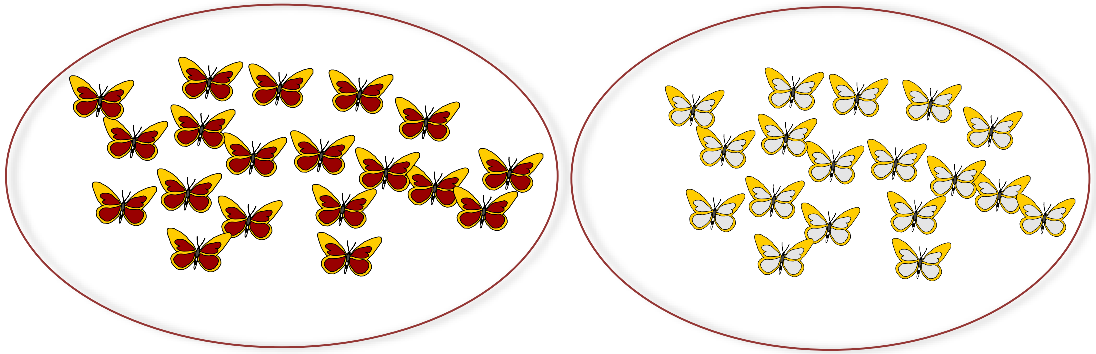
Mutation
Individual level



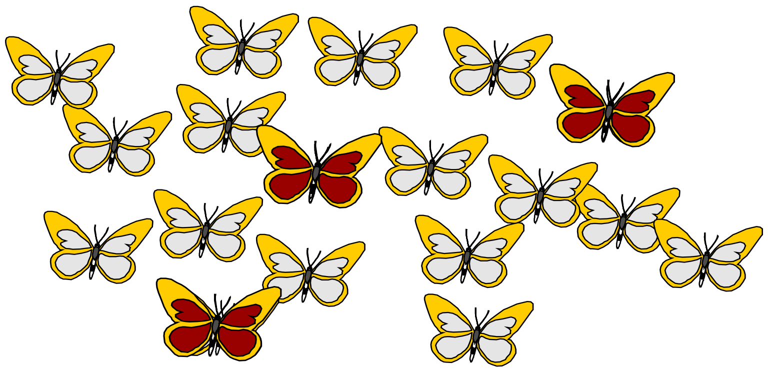
$K = \mu_0$

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

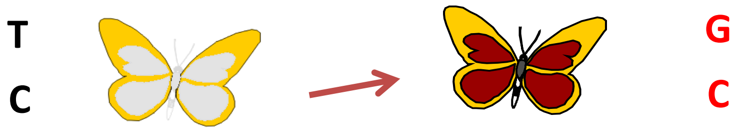
Divergence
Species level



Polymorphism
Population level



Mutation
Individual level

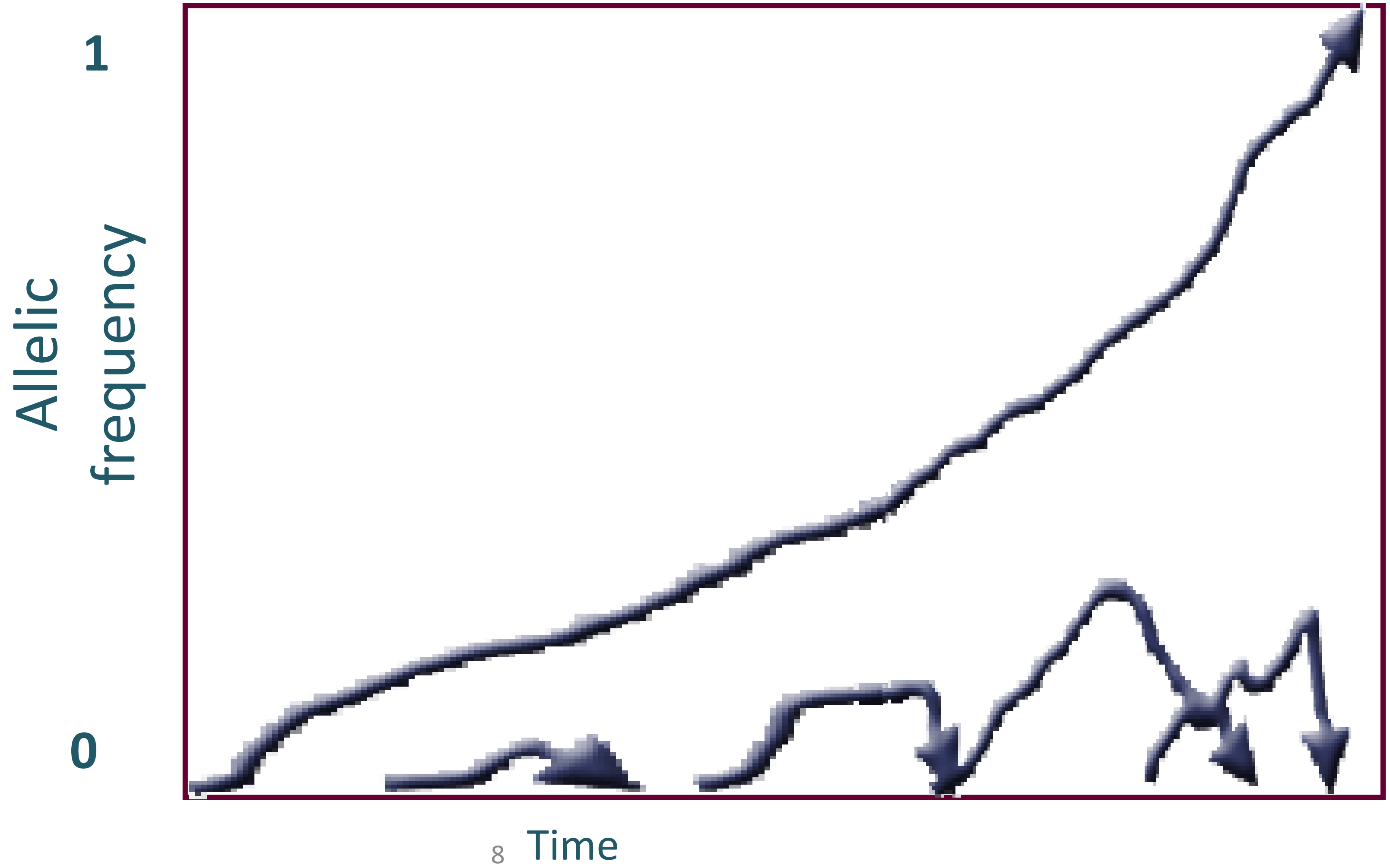


Population Genetics

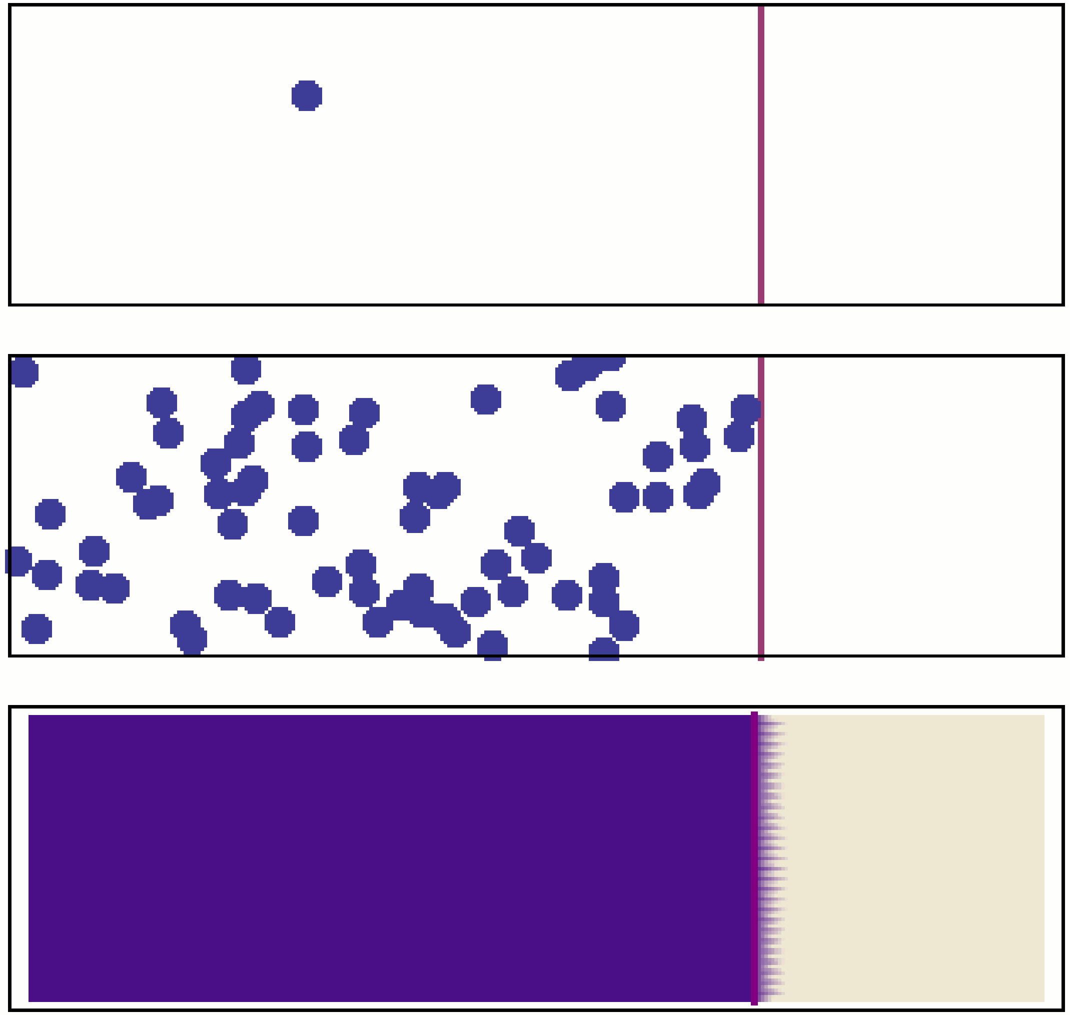
$K = \mu_0$

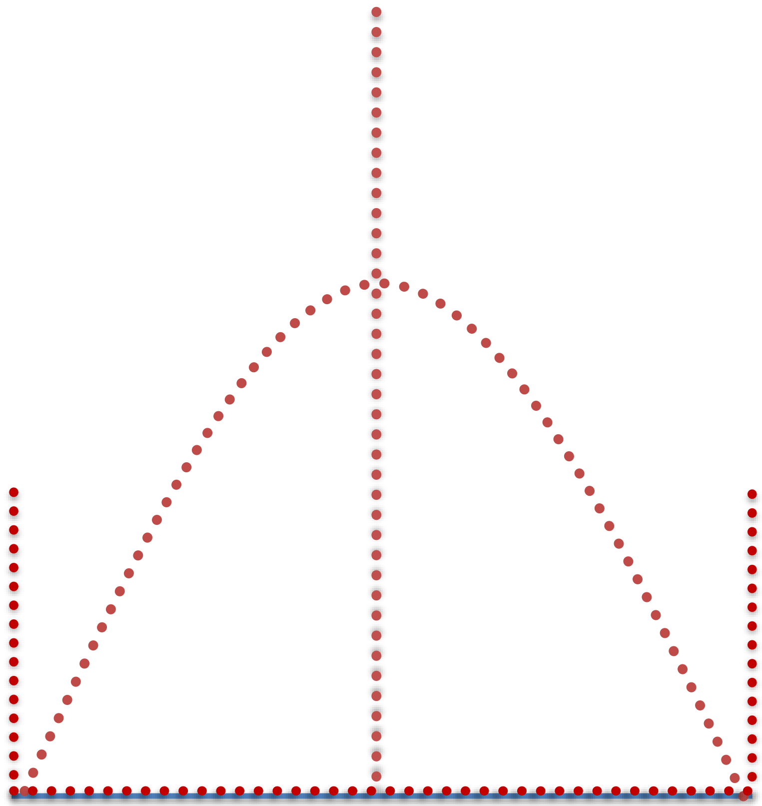
How does allelic frequency change over time?

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



$K = \mu_0$





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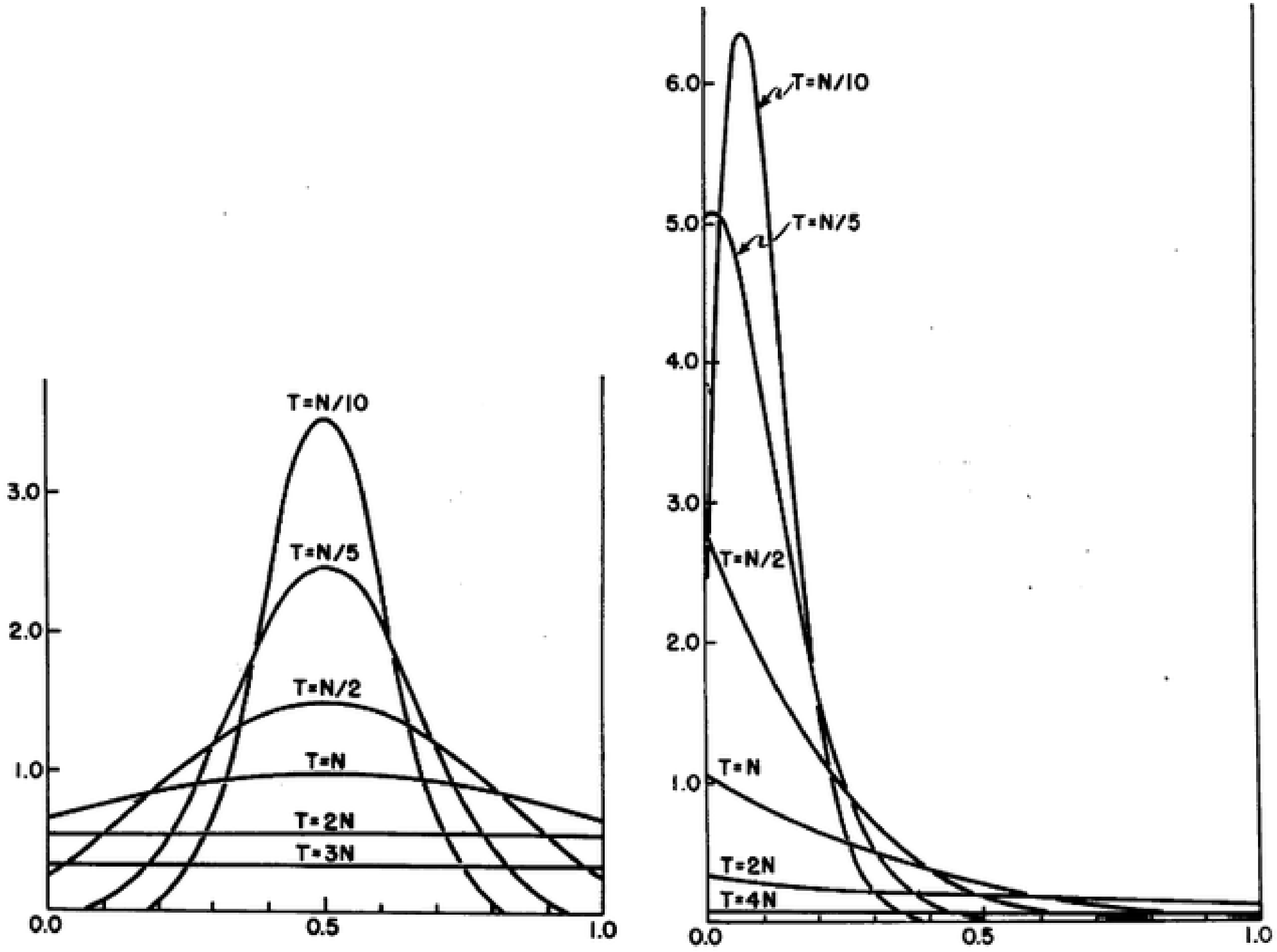


FIGS. 1–2.—The processes of the change in the probability distribution of heterallelic classes, due to random sampling of gametes in reproduction. It is assumed that the population starts from the gene frequency 0.5 in Fig. 1 (left) and 0.1 in Fig. 2 (right). t = time in generation; N = effective size of the population; abscissa is gene frequency; ordinate is probability density.

$\phi(x,t)$ The probability that the population have allele frequency x time t

$M(x)$ the probability that the frequency increased from x by dx, due to mutation/selection

$V(x)/2$ The probability of dx increase or decrease due to drift

$$\frac{\partial}{\partial t}\phi(x,t) = -\frac{\partial}{\partial x}\left[M(x)\phi(x,t)\right] - \frac{1}{2}\frac{\partial}{\partial x^2}\left[V(x)\phi(x,t)\right]$$

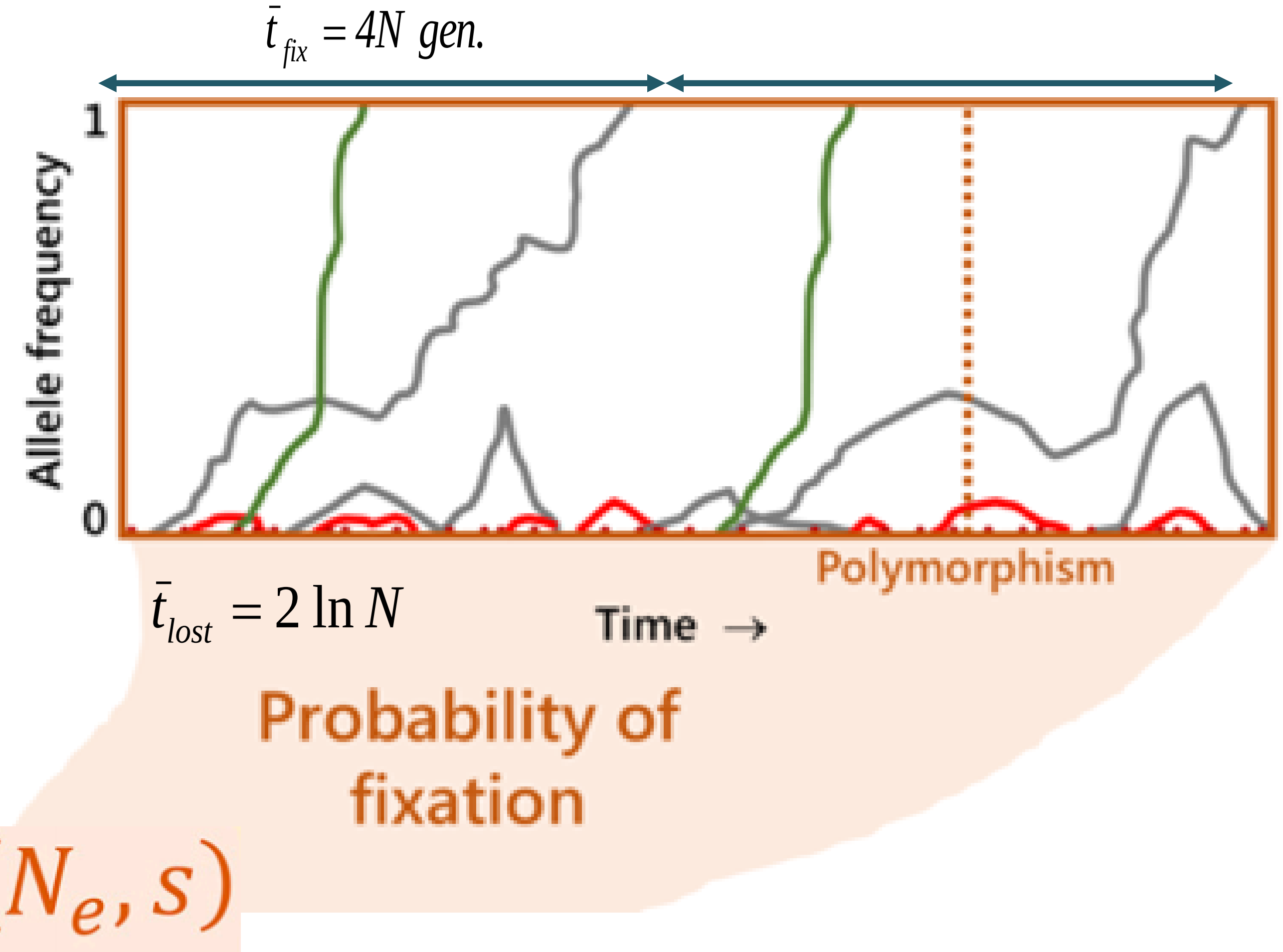
$K = \mu_0$

Kimura M., 1955. Stochastic processes and distribution of gene frequencies under natural selection. Cold Spring Harb. Symp. Quant. Biol. 20: 33–55

Probability of fixation of new mutations in populations

Motoo Kimura (1957)

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

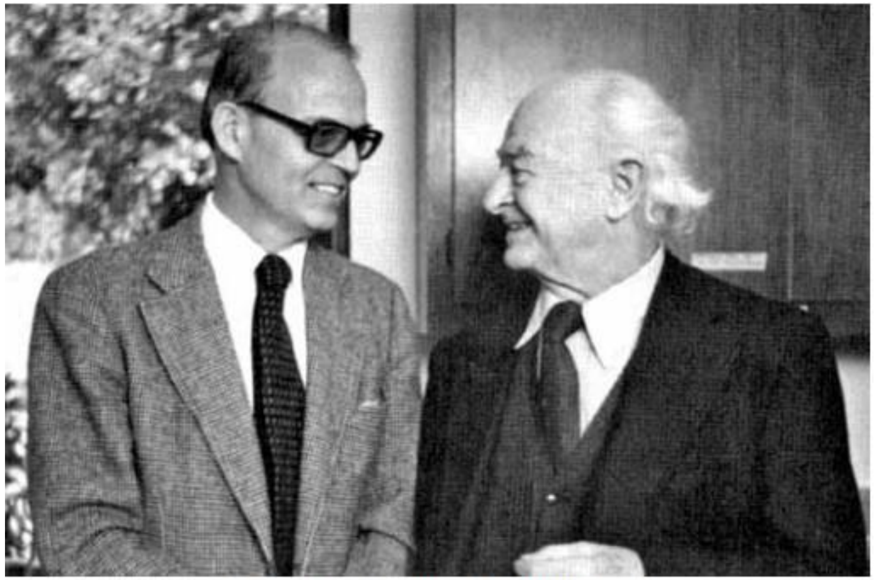


$K = \mu_0$

60’

- **Molecular clock in divergent amino acid sequences (1965)**

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



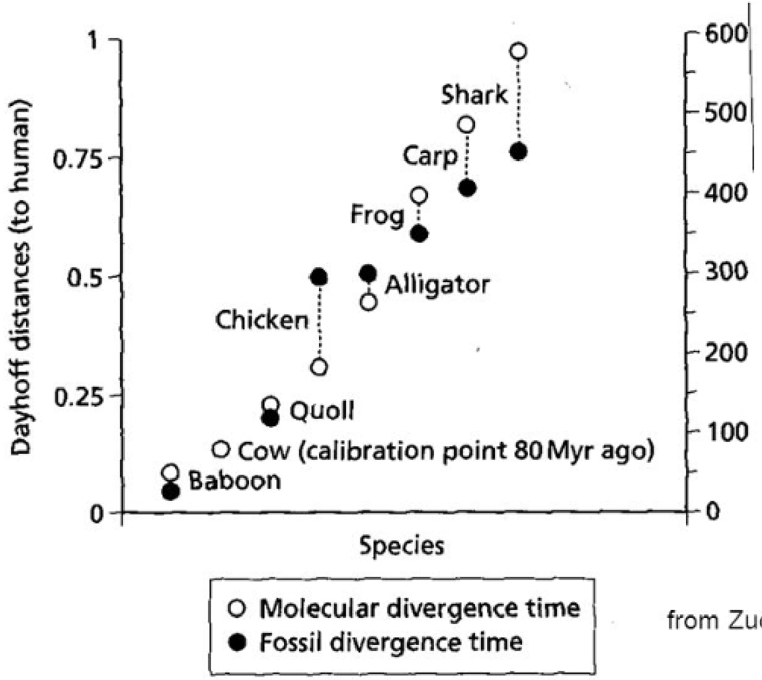
Dr. Emile Zuckerkandl and Dr. Linus Pauling

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*[1]

R. C. LEWONTIN AND J. L. HUBBY

Department of Zoology, University of Chicago, Chicago, Illinois

Received March 30, 1966



Hemoglobin

from Zuckerkandl and Pauling (1965)

Harris H., 1966 Enzyme polymorphisms in man. Proc R Soc Lond B Biol Sci **164**: 298–310

R. C. Lewontin

$K = \mu_0$

1968

Evolutionary Rate at the Molecular Level

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

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NATURE. VOL. 217. FEBRUARY 17. 1968 625

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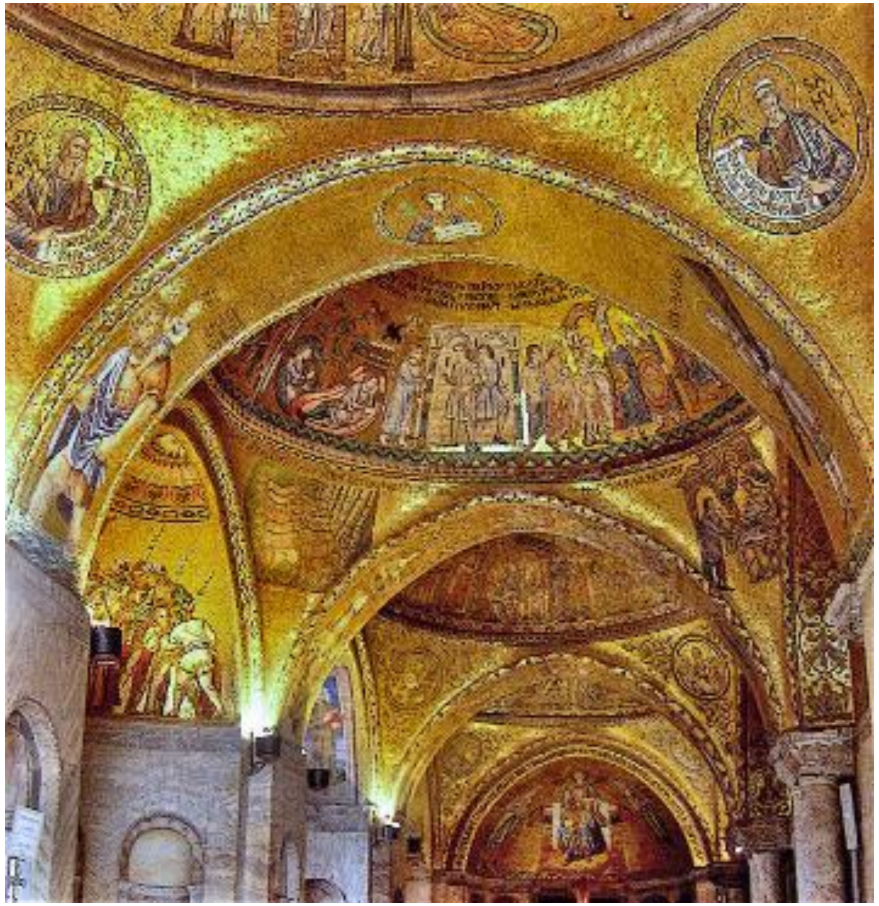
$K = \mu_0$

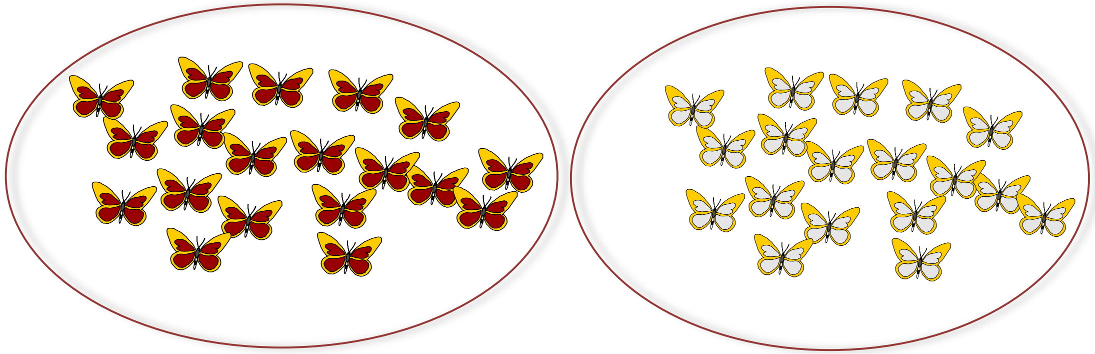
Antonio Barbadilla

Panseleccionism



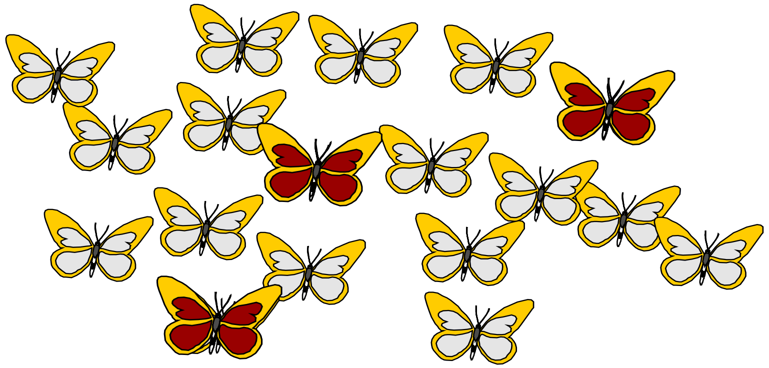
Evolution is the process of conversion of individual variation into species variation

Divergence
Species level



Population genetics: the kinematics and dynamics of evolutionary changes

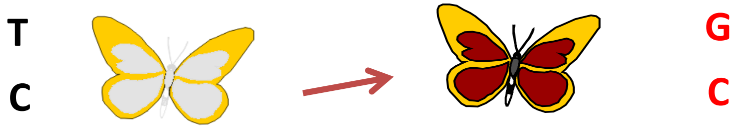
Polymorphism
Population level



Evolutionary forces

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

Mutation
Individual level



$K = \mu_0$

Science. 1969 May 16;164(3881):788-98. Non-Darwinian evolution.
King JL, **Jukes** TH.

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.

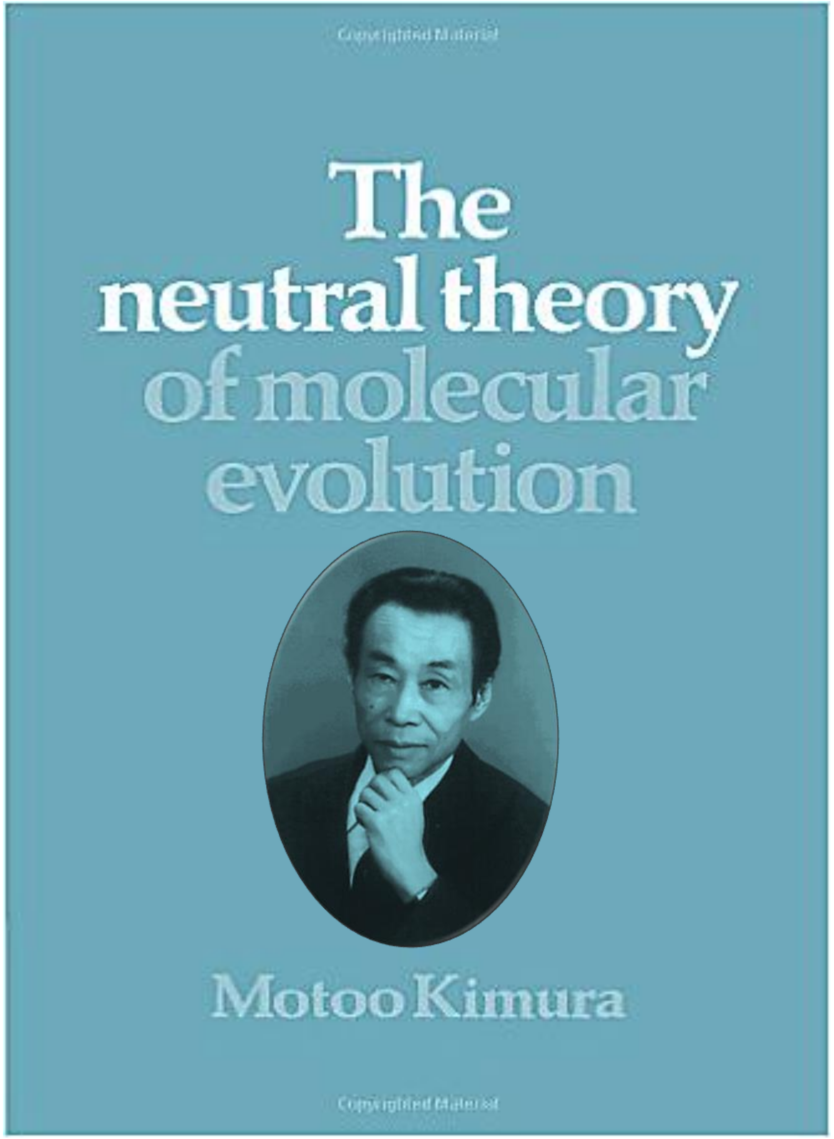
The view that mutations cannot be selectively neutral is not confined to organismal evolutionists. Smith (*3*) states:

> 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.

Dr. King is a biophysicist and geneticist for the Donner Laboratory and Dr. Jukes is associate director of the Space Sciences Laboratory, University of California, Berkeley 94720.

Dietrich, Michael R. (1994-03-01). "The origins of the neutral theory of molecular evolution". *Journal of the History of Biology*. **27** (1): 21–59

The "neutralist–selectionist" controversy



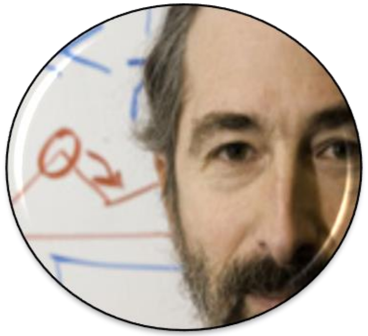
1983

Tomoko Ohta
1933

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

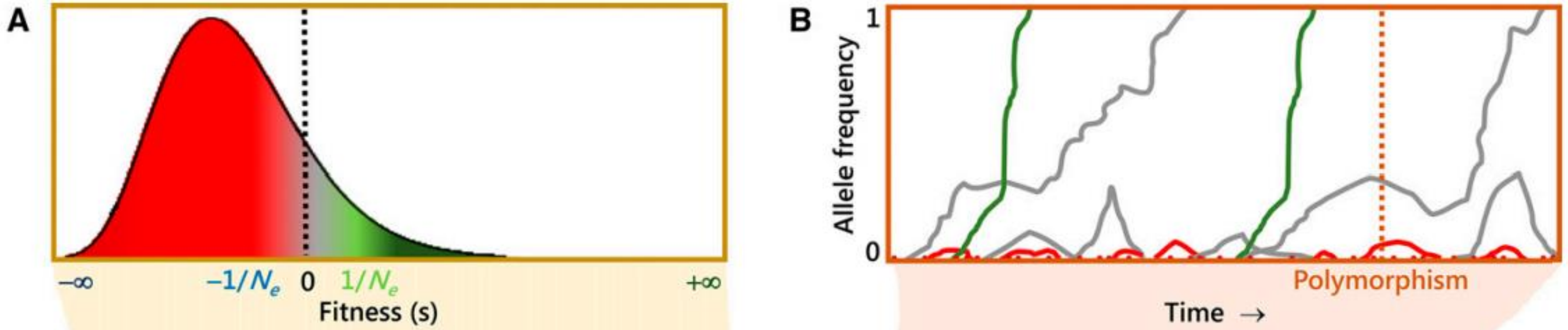
Distinctive features of Neutral Theory

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

Distinctive features of Neutral Theory

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

The general equation of molecular evolution



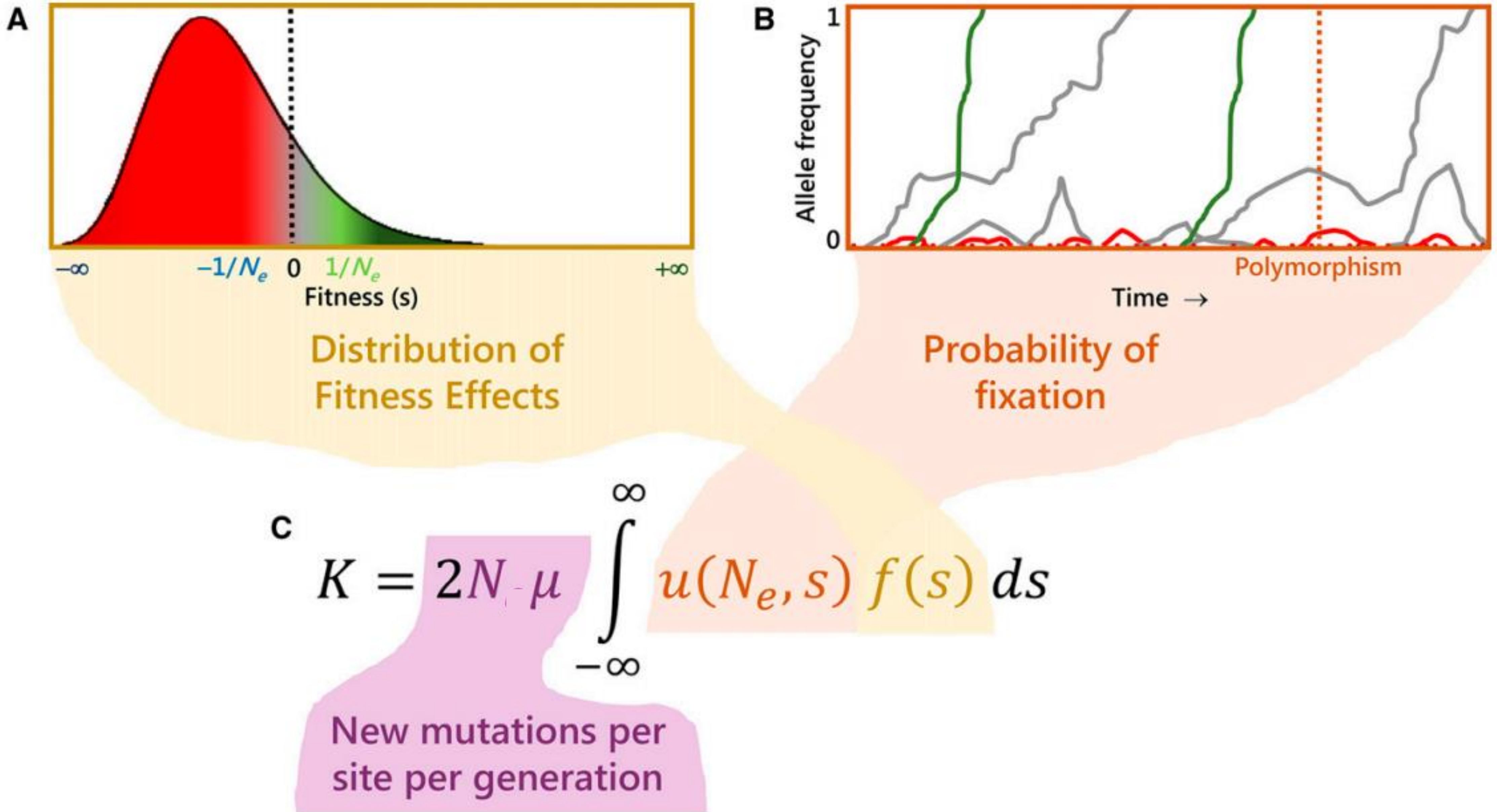
Distribution of Fitness Effects

Probability of fixation

K_i = Prob fixation new mutant *i*

$$K_i = u(N_e, s)\, f(s)\, ds$$

The general equation of molecular evolution



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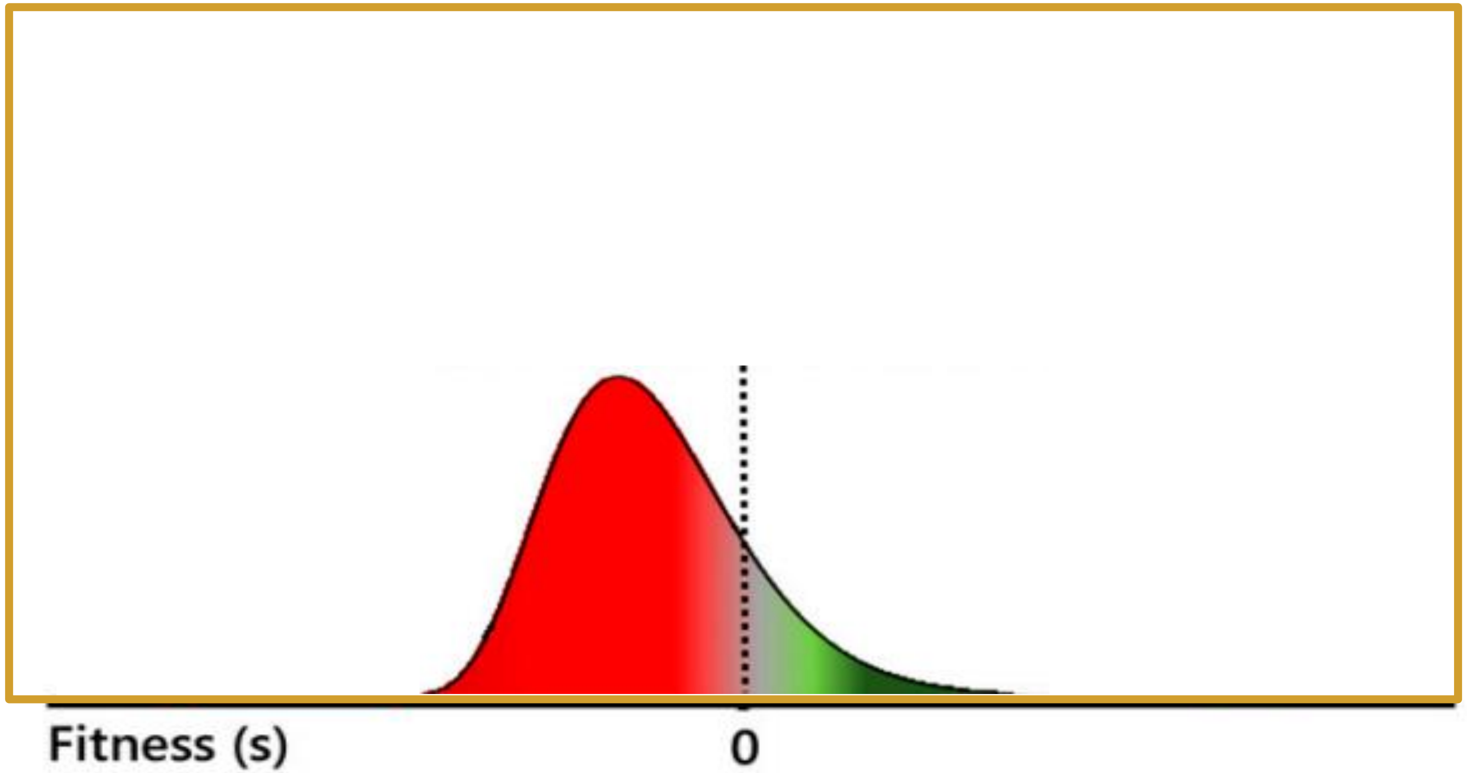
Neutral Theory of Molecular Evolution (1968)

Assumption

*New mutations are mainly **neutral** or **strongly deleterious***



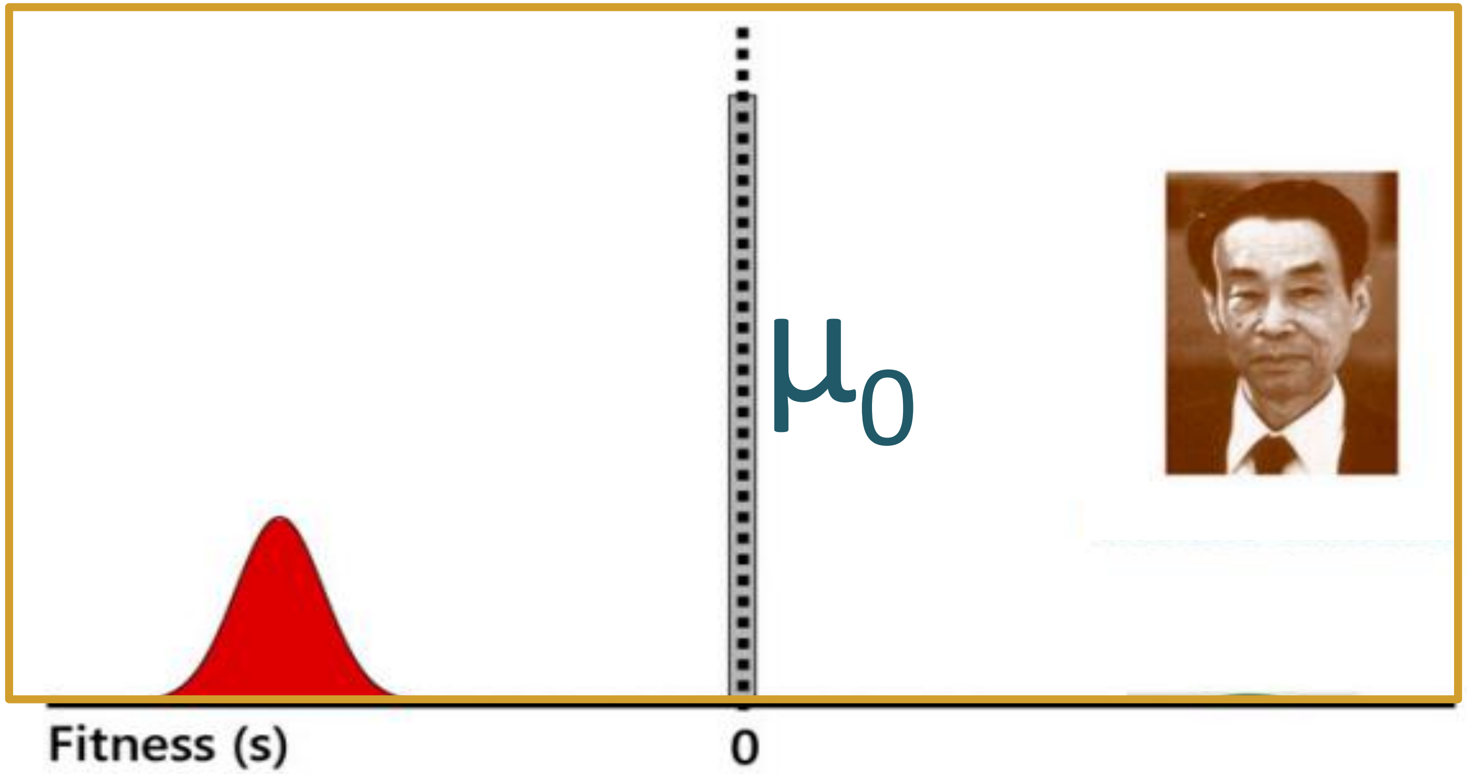
DFE (Distribution fitness effect of new mutation) of Kimura's Neutral Theory

$K = \mu_0$

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

$K = \mu_0$

New mutations entering each generation in the population

$$K = \frac{1}{2\cancel{N}} \, 2\cancel{N}\mu_0$$

Probability of fixation

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

$K = \mu_0$

Theorem

$$K = \mu_0$$

Substitution rate
or
Fixation rate
or
Evolutionary rate

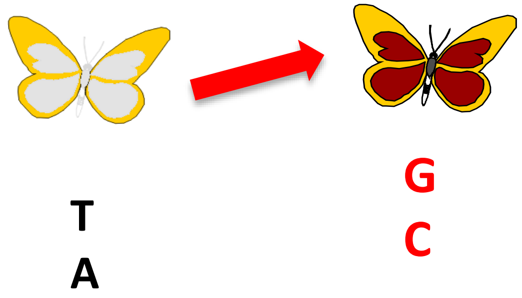
=

neutral mutation rate

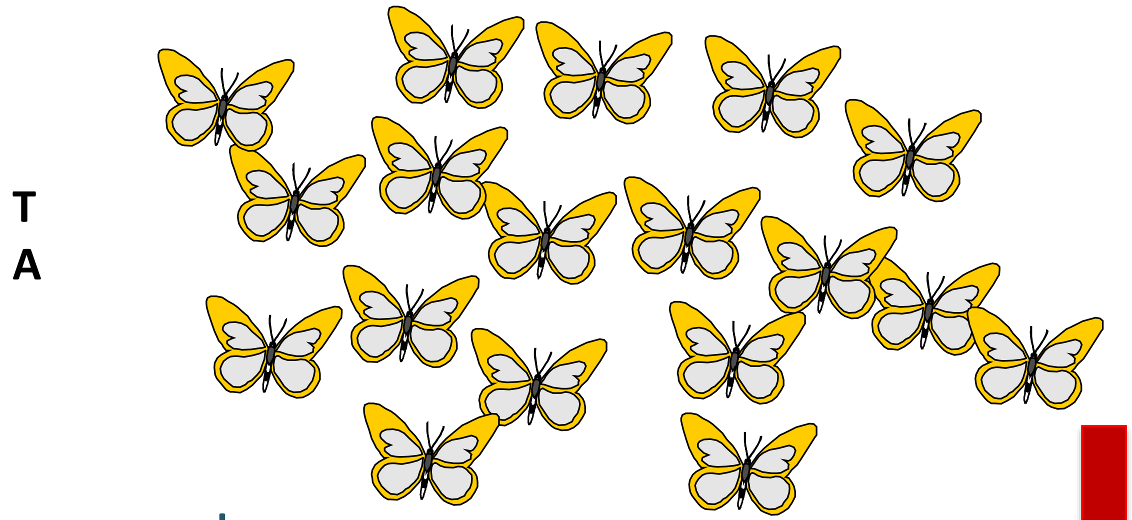
$k = \mu_0$

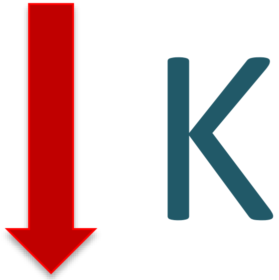
Neutral mutation rate

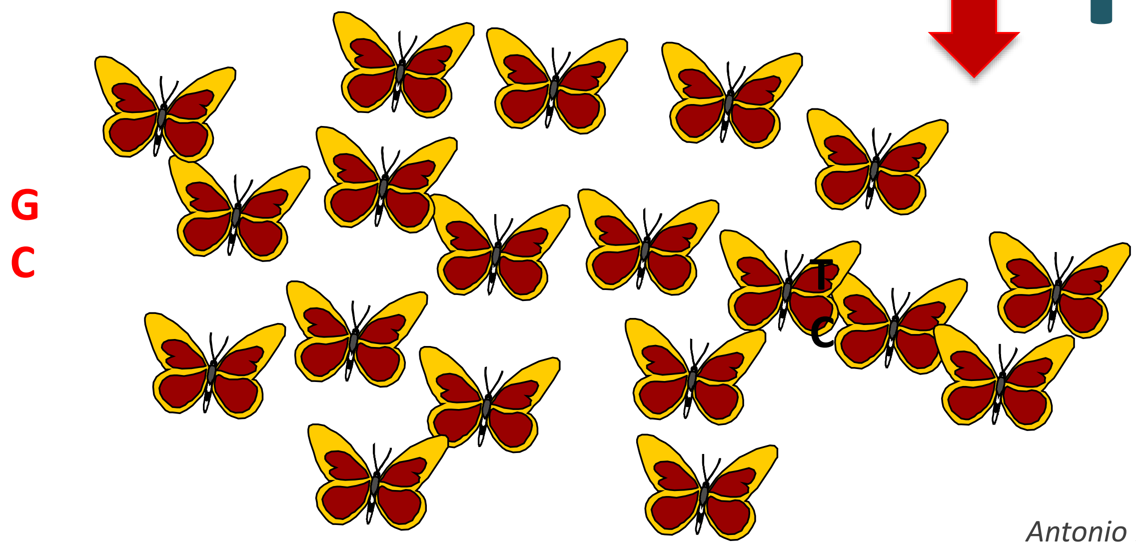
$$\mu_0$$

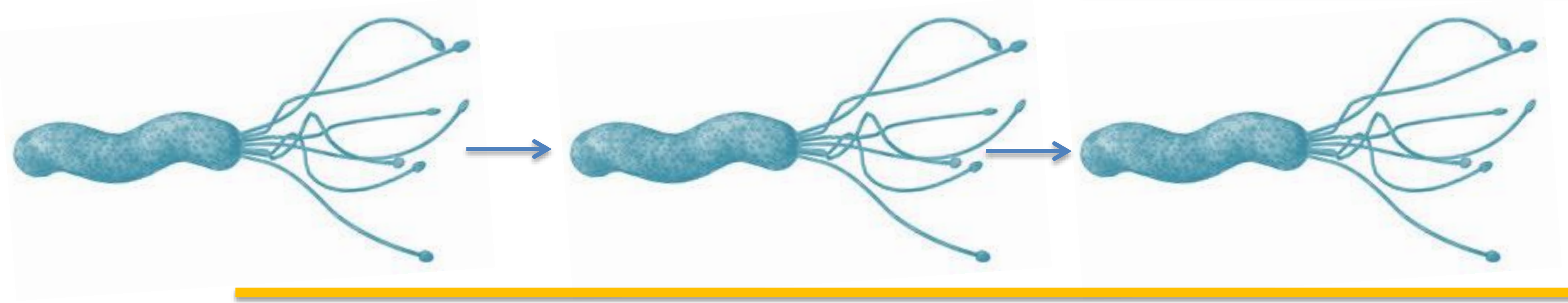


Evolutionary rate









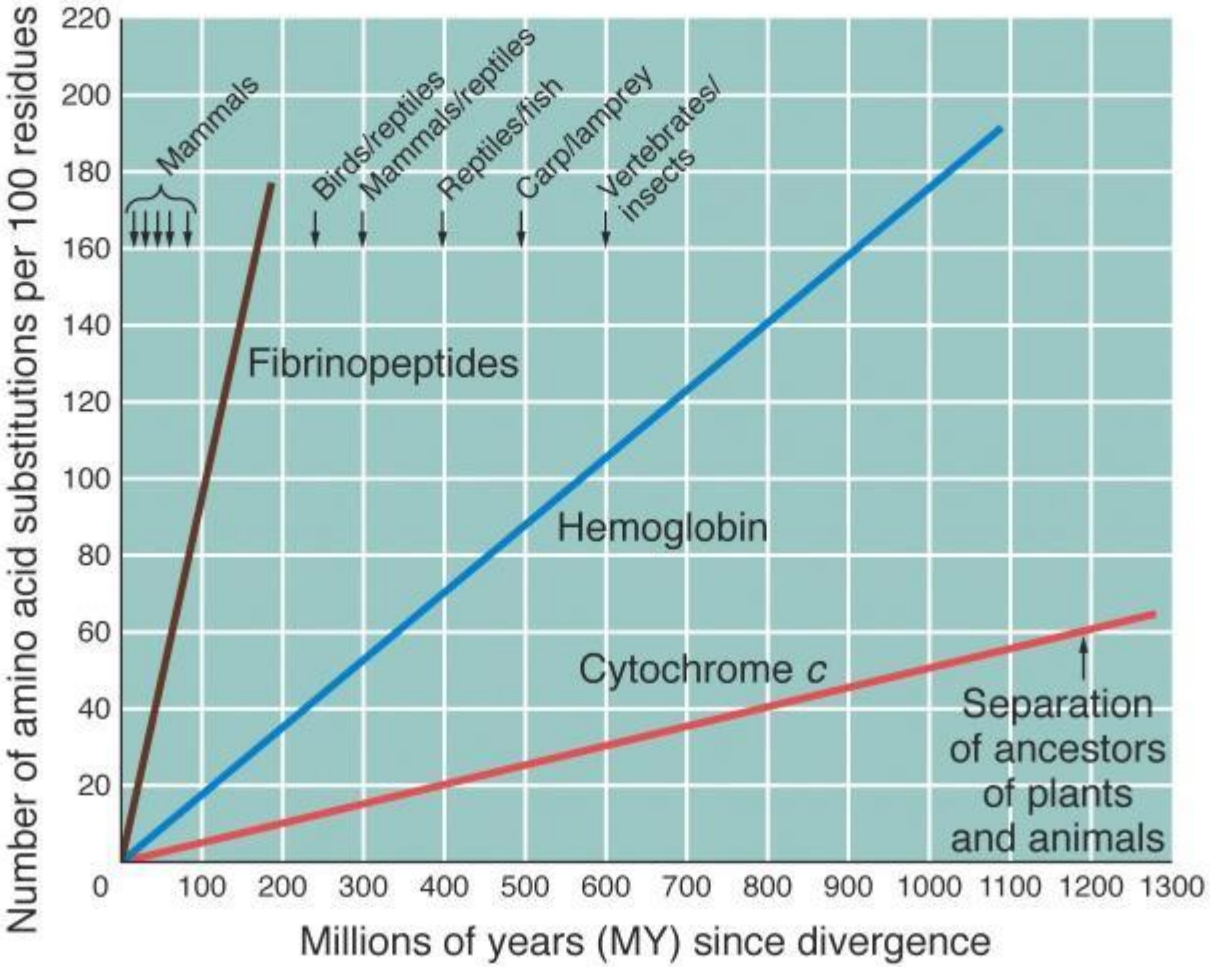
$$K = \mu_0$$

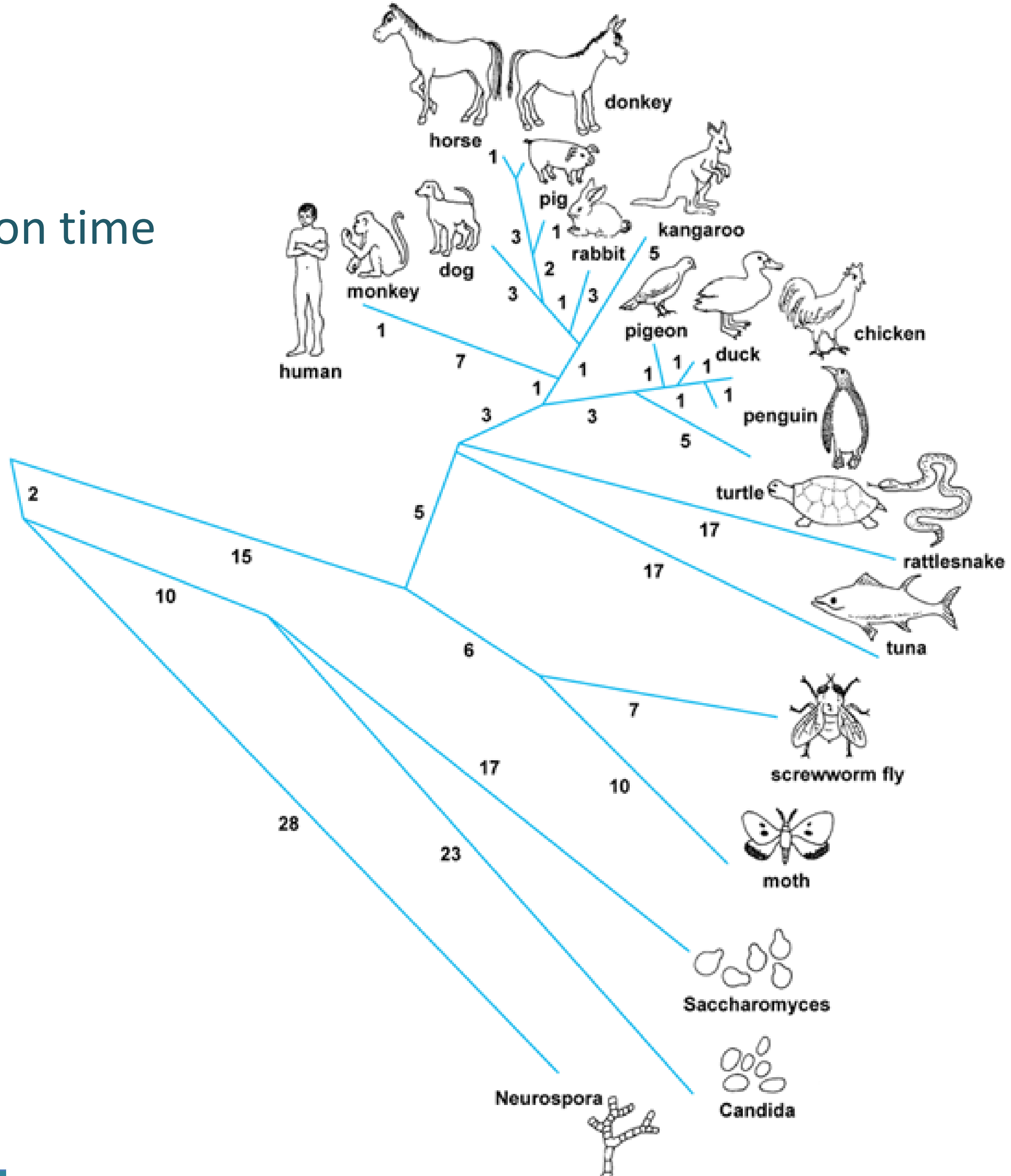
Molecular Clock

Émile **Zuckerkandl** and Linus **Pauling (1965)**

- Divergence increases linearly over generation time

$$K = \mu_0 \rightarrow D = 2T\mu_0$$





K =

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

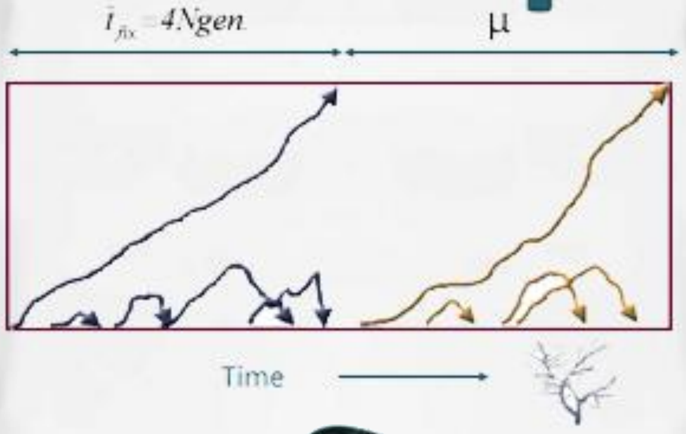
$$K = \mu_0$$

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

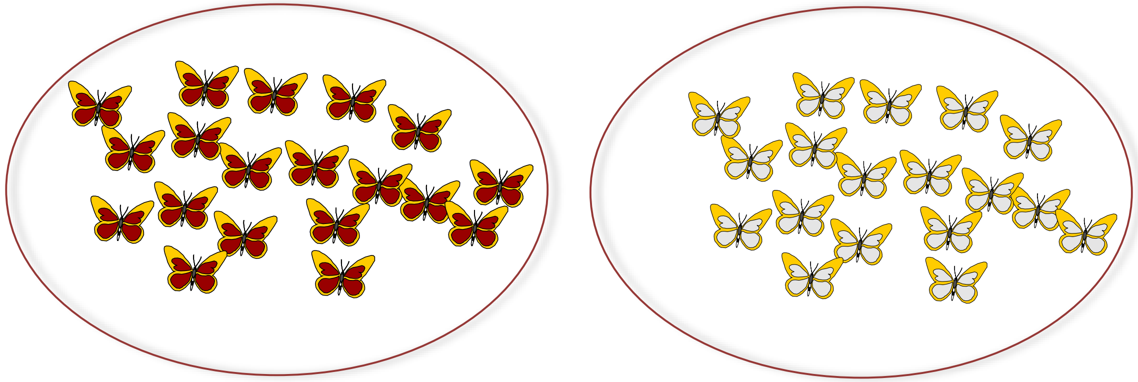
Distinctive features of Neutral Theory

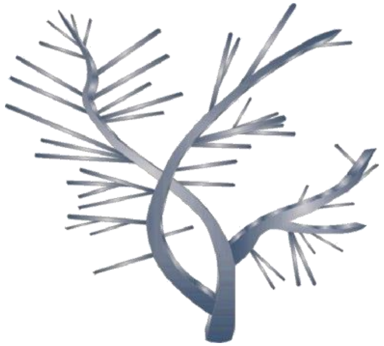
- Simplicity
- **Intelligibility**
- Robustness
- Testable theoretical predictions
- Chance in evolution
- Facilitator of adaptation

Intelligibility (descend with modification made clear)

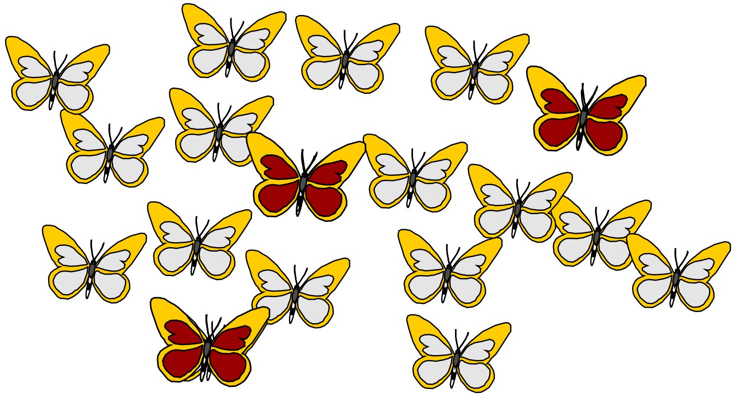
Evolution is the process of conversion of individual variation into species variation

Divergence
Species level

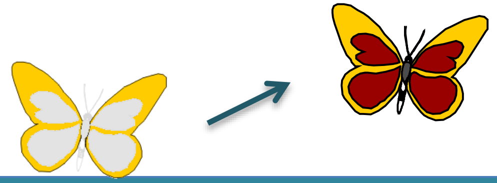




Polymorphism
Population level



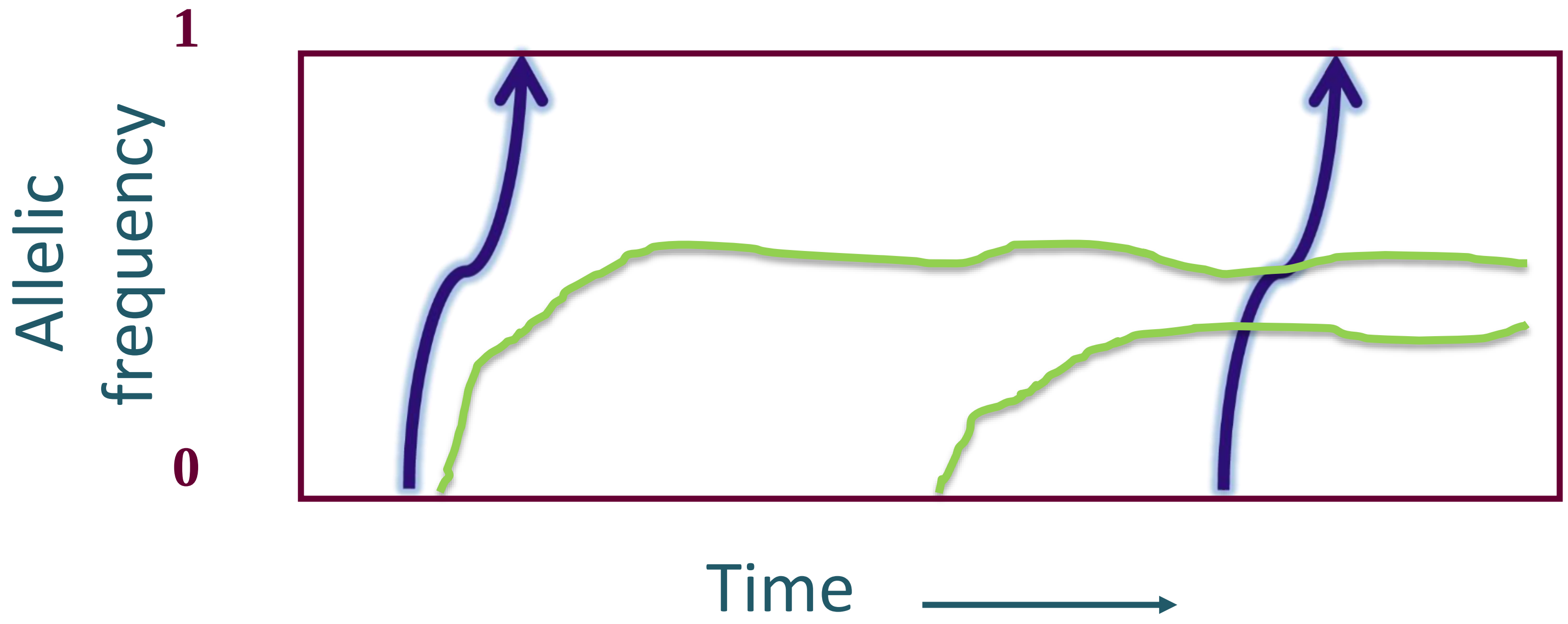
Mutation
Individual level



$K = \mu_0$

Intelligibility (descend with modification made clear)

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



Selectionist view before Neutral theory

- Polymorphism (overdominace) Dobzhansky's view.
- Divergence (positive Darwinian selection)

Intelligibility (descend with modification made clear)

Polymorphism within species as a transient phase of molecular evolution

NATURE VOL. 229 FEBRUARY 12 1971

Protein Polymorphism as a Phase of Molecular Evolution

MOTOO KIMURA & TOMOKO OHTA

National Institute of Genetics, Mishima, Shizuoka-ken

It is proposed that random genetic drift of neutral mutations in finite populations can account for observed protein polymorphisms.

the difference of the evolutionary rates among different molecules can be explained by assuming that the different fraction of mutants is neutral depending on the functional requirement of the molecules.

On the other hand, it can be shown that if the mutant substitution is carried out principally by natural selection

$$k = 4N_e s_1 u \qquad (2)$$

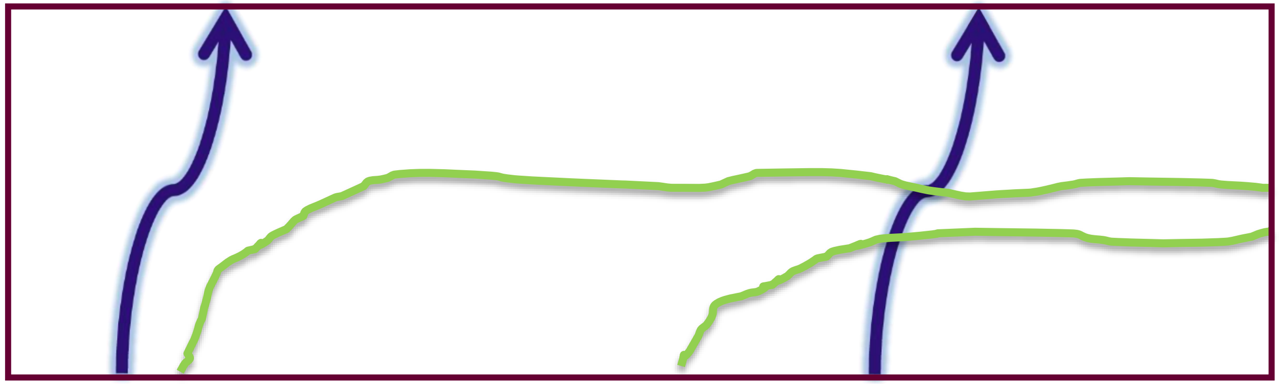
$K = \mu_0$

Intelligibility (descend with modification made clear)

1

Allelic frequency

0



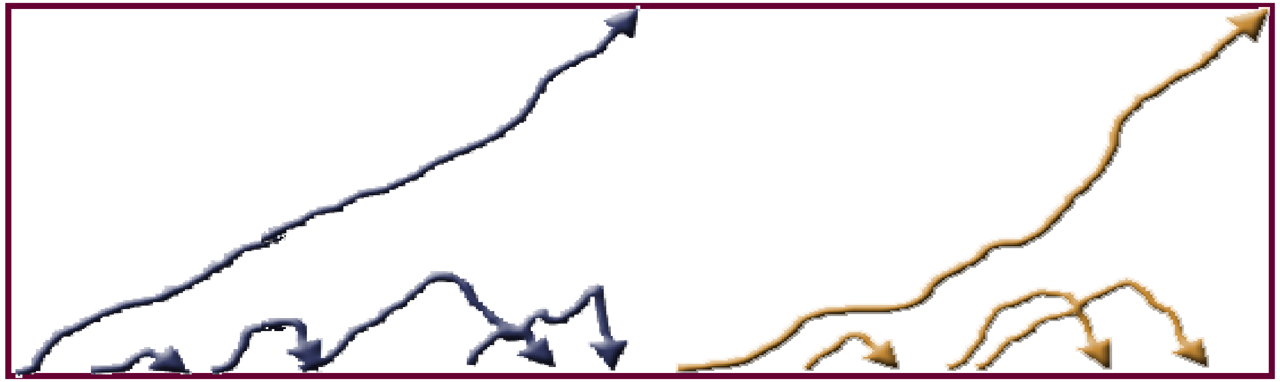
Selectionist view

- Polymorphism (overdominace)
- Divergence (positive Darwinian selection)

1

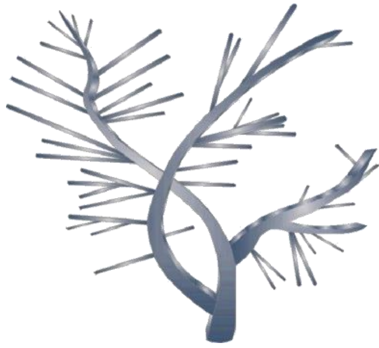
Allelic frequency

0



Neutral view

Polymorphism as a transient phase of molecular evolution



Time →

$K = \mu_0$

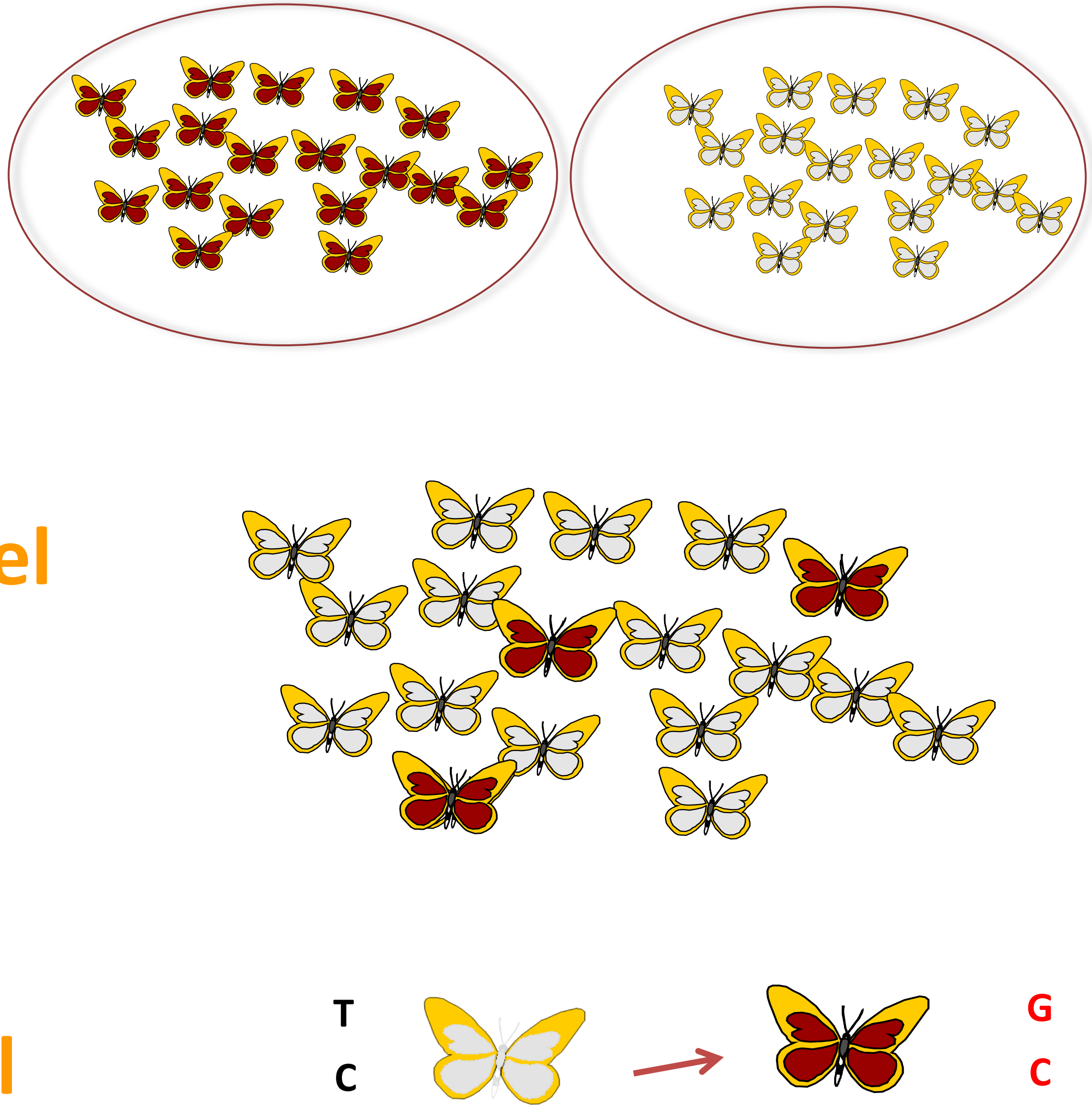
Antonio Barbadilla

Polymorphism as a transient phase of molecular evolution

Divergence
Species level

Polymorphism
Population level

Mutation
Individual level

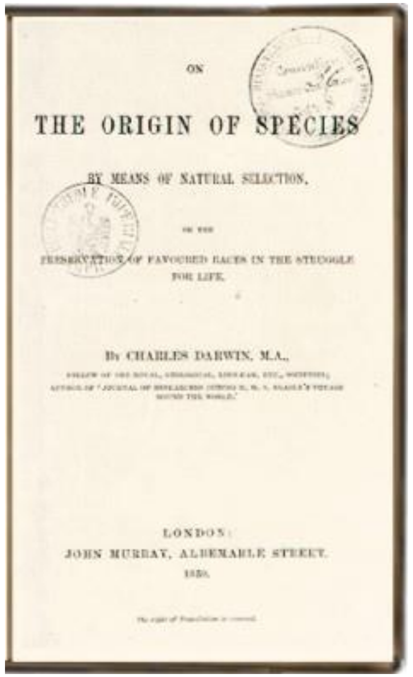


Molecular Evolution

Population Genetics

$K = \mu_0$

Antonio Barbadilla


ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

BY CHARLES DARWIN, M.A.,

LONDON:

JOHN MURRAY, ALBEMARLE STREET.

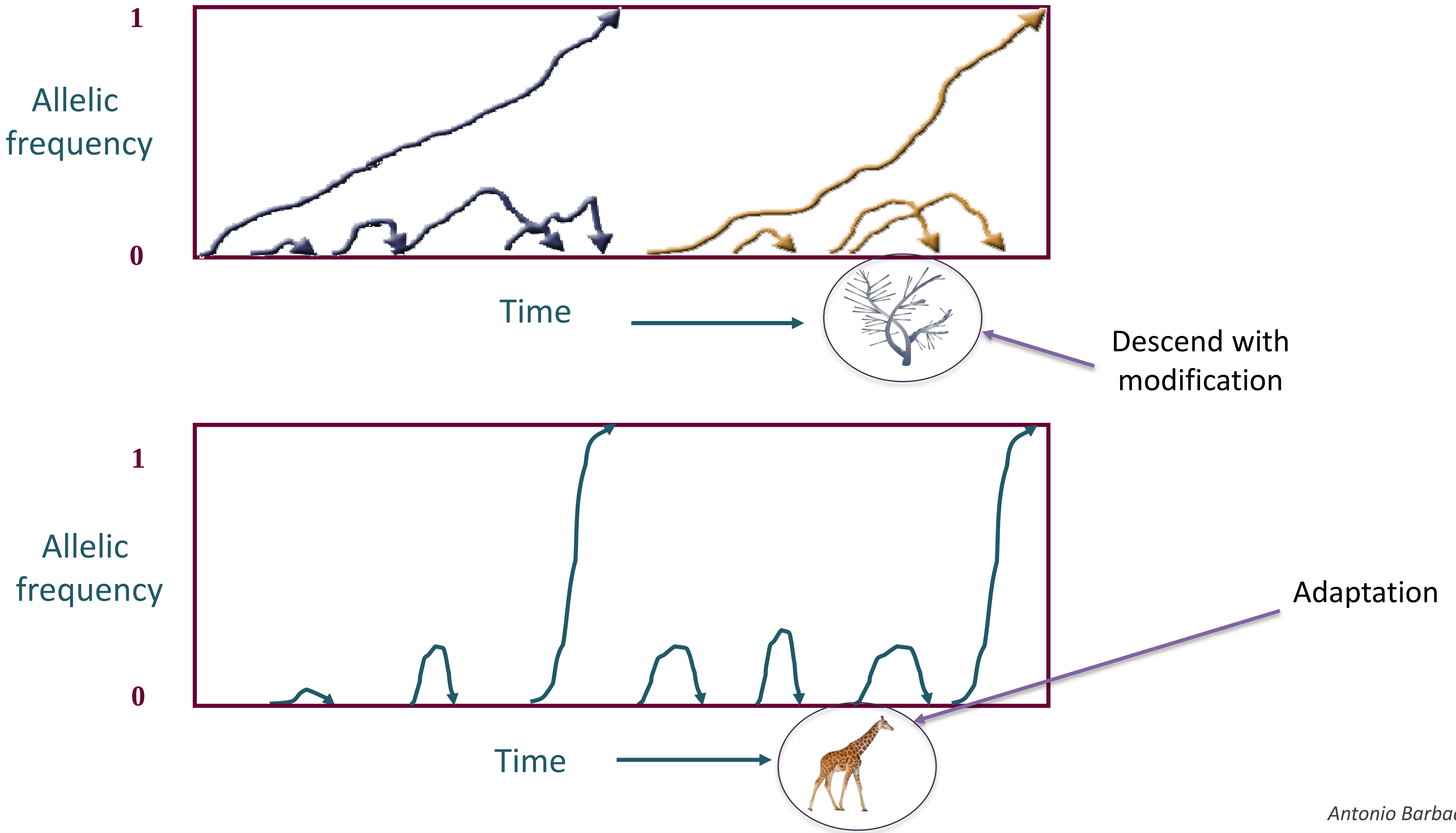
1859.

Two main contributions of the Origin

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

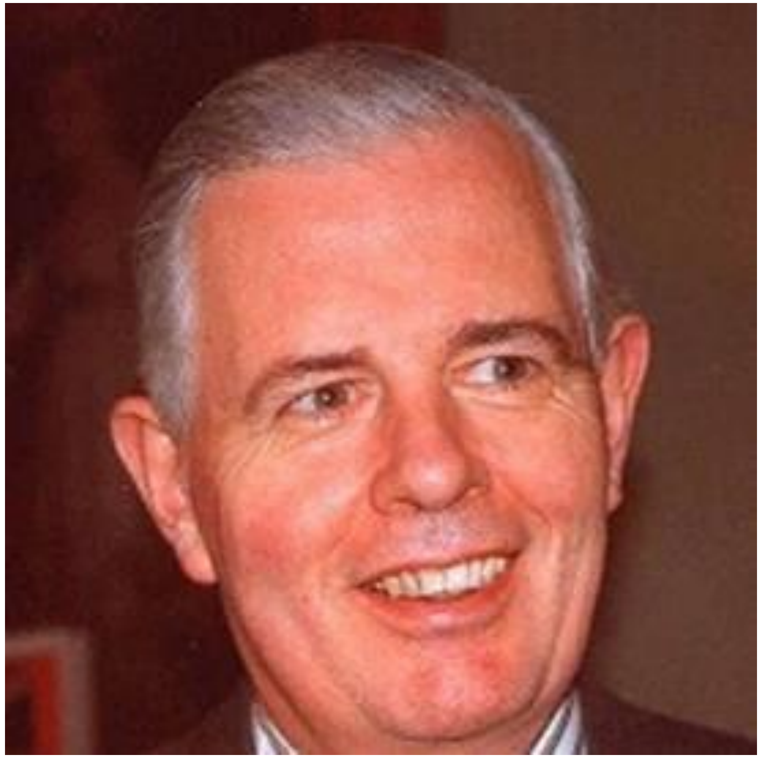
2. Adaptations result from natural selection

Population dynamics of neutral and adaptive mutations



$K = \mu_0$

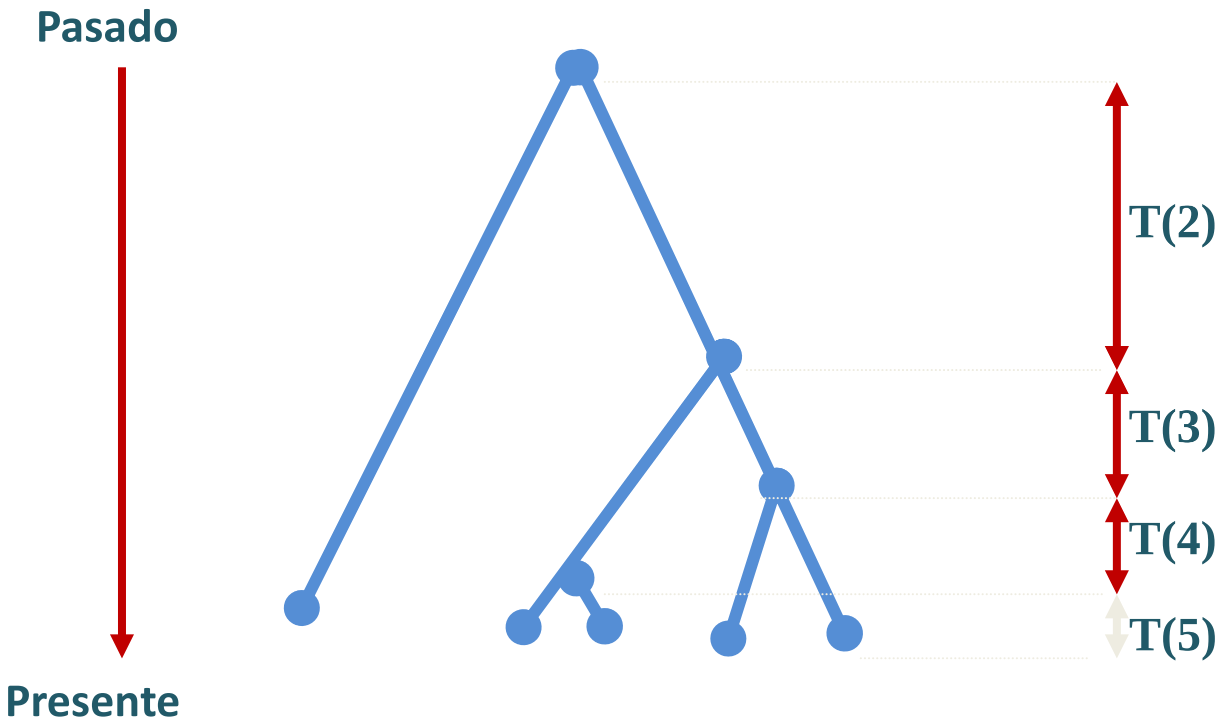
Neutral theory inspired coalescent theory: The genealogy of genes

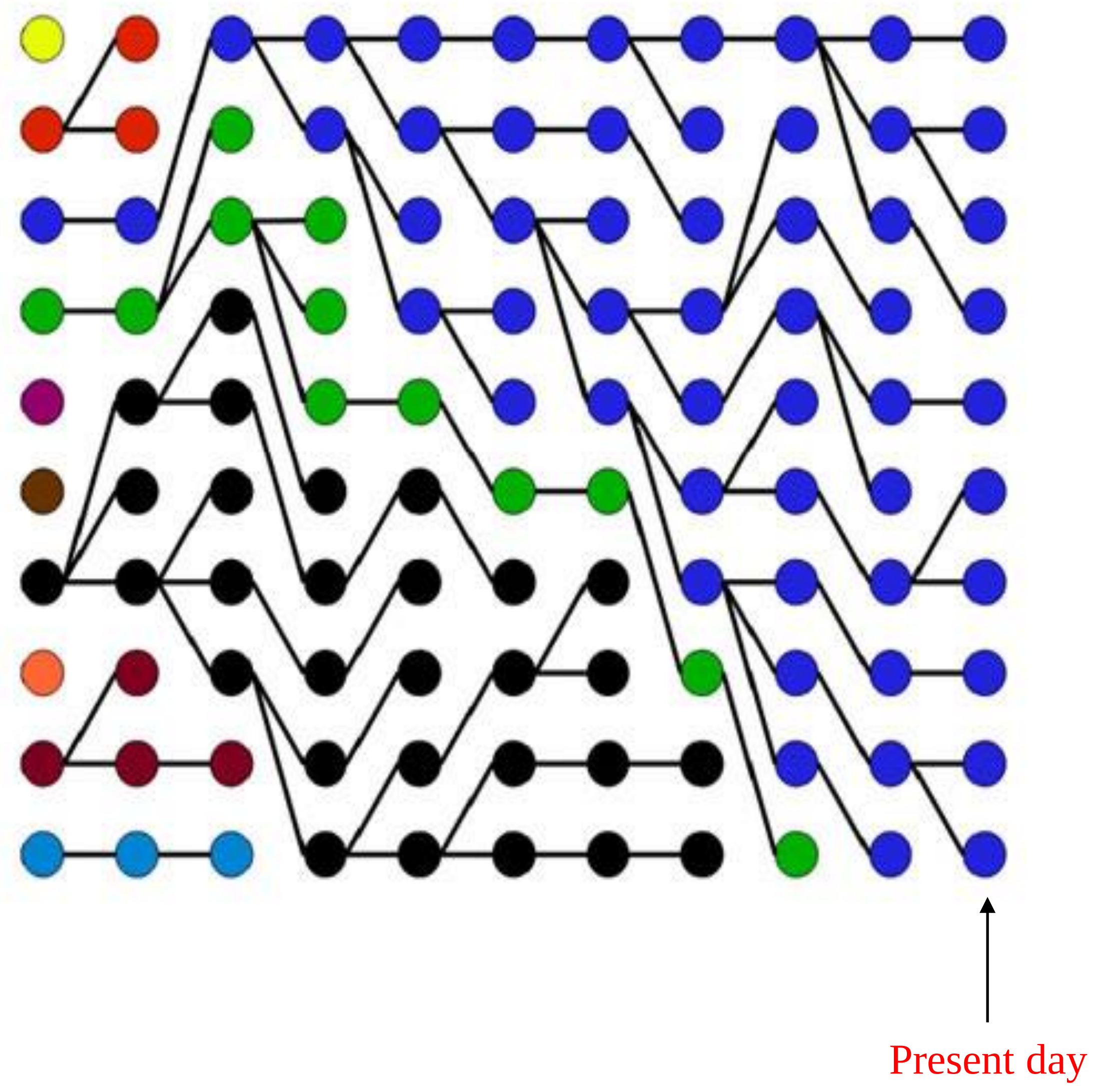


Sir John Kingman - born at 1939

Kingman, J. F. C. (1980). *Mathematics of Genetic Diversity*. Society for Industrial and Applied Mathematics.
Kingman, J. F. C. (1982). "On the Genealogy of Large Populations". *Journal of Applied Probability*. **19**: 27–43.

Neutral theory inspired coalescent theory





$K = \mu_0$

Kingman, J. F. C. (1980). *Mathematics of Genetic Diversity*. Society for Industrial and Applied Mathematics.
Kingman, J. F. C. (1982). "On the Genealogy of Large Populations". *Journal of Applied Probability*. **19**: 27–43.

Distinctive features of Neutral Theory

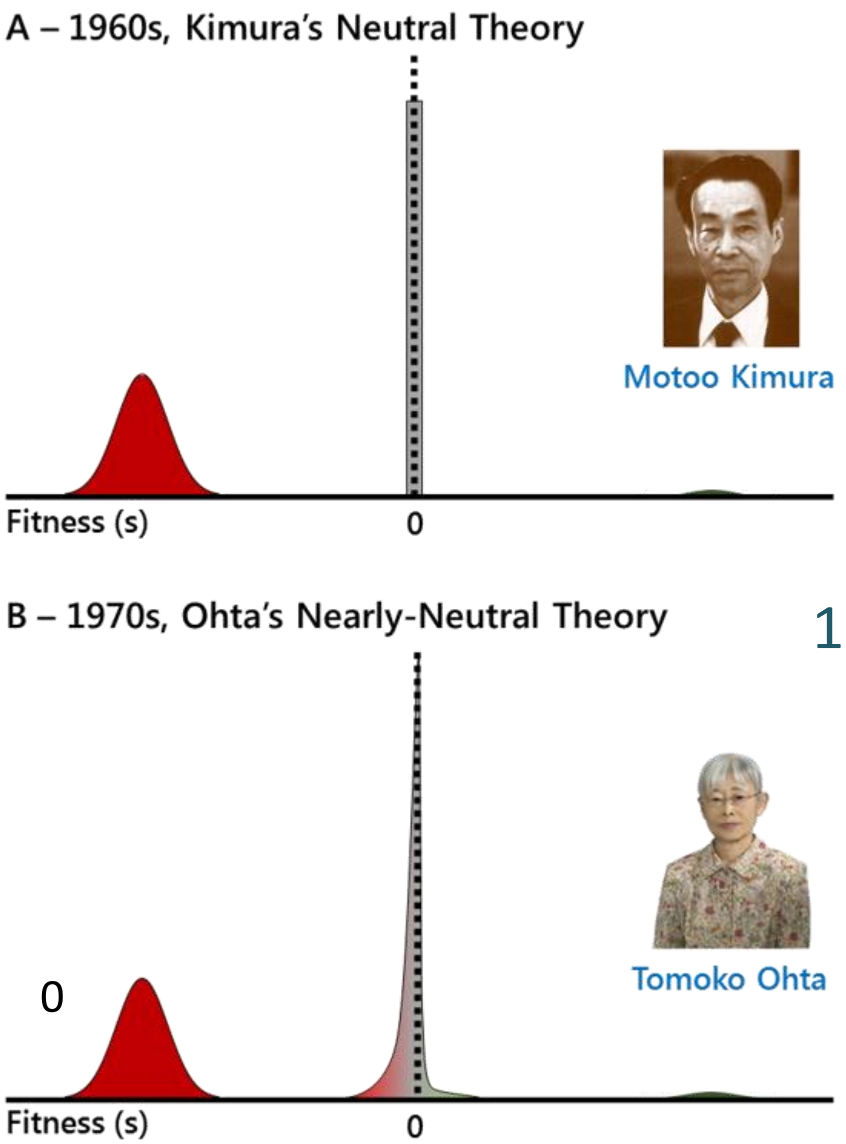
- Simplicity
- Intelligibility
- **Robustness**
- Testable theoretical predictions
- Chance in evolution
- Facilitator of adaptation

The nearly-neutral theory

Ohta’s extension to Kimura’s neutral theory

Mutations are mainly ***neutral*** *or* ***slightly deleterious*** *or* ***strongly deleterious***

1968



1973

DFE (Distribution fitness effect of new mutations)

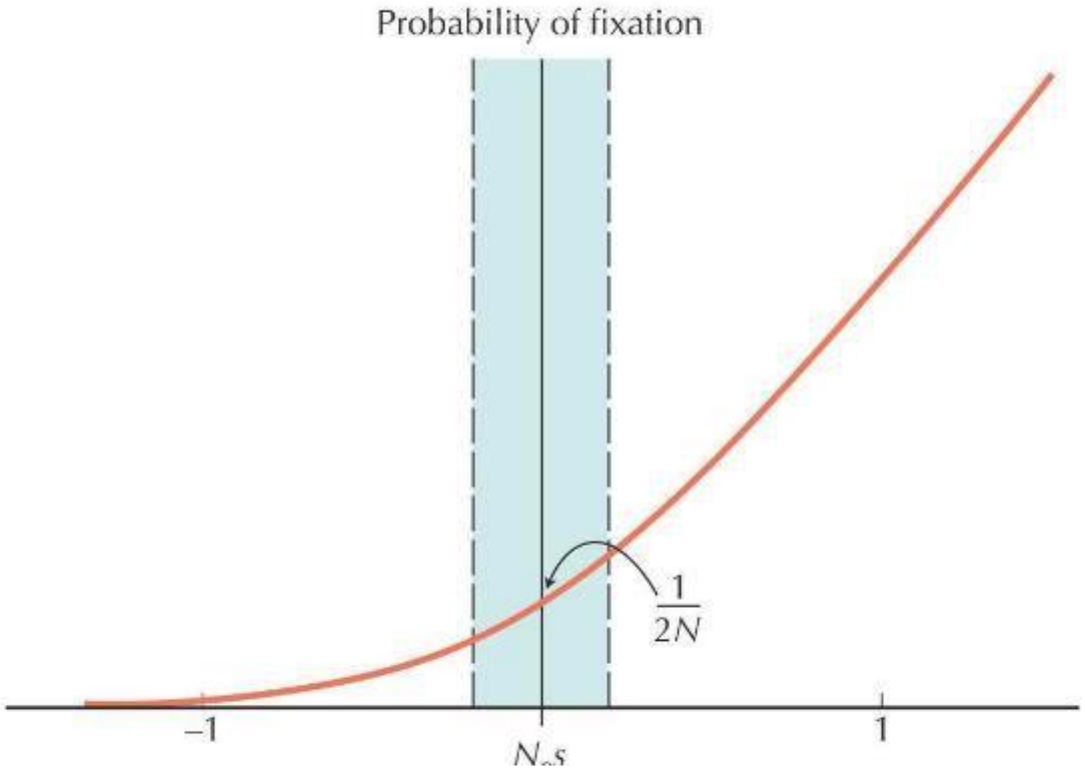
$K = \mu_0$

Ohta, T. 1973. **Slightly deleterious mutant substitutions in evolution**, Nature 246, 96 98. 141

The nearly-neutral theory

Effective selection -> *N s*

Interplay *N* and s



i. $|N s| \leq 1$ effectively neutral realm

ii. $10 \leq |N s| \geq 1$ nearly neutral

iii. $|N s| \geq 10$ strong selection

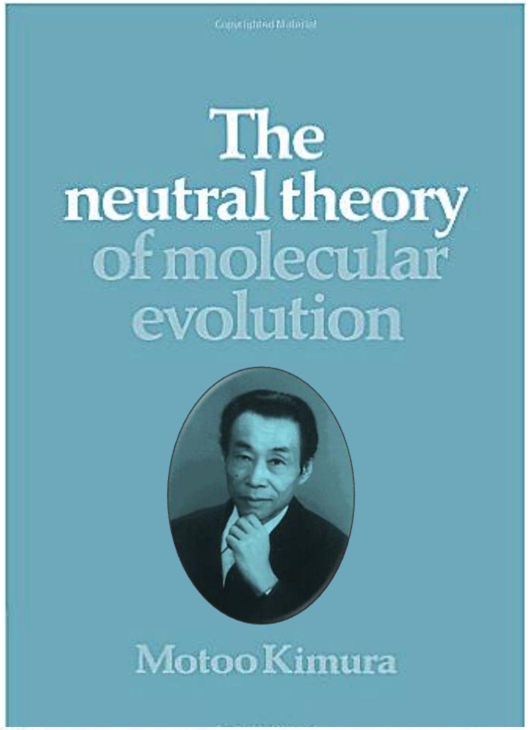
- Generation time effect on K ($K = \mu_0$)
- Frequency spectrum
- Codon bias
- Compensatory mutations

$K = \mu_0$

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

$$\mu_0 = (1\text{-}f)\ \mu$$

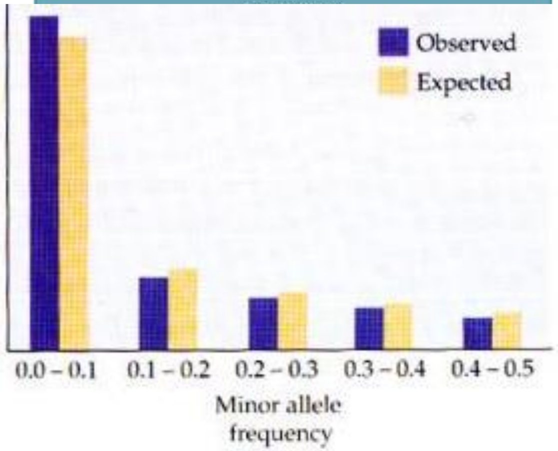
f = Constraint index

Define the fraction of effectively neutral mutations

Divergence $K = \mu_0$

Polymorphism: nucleotide diversity (π)

$$\pi = \Theta = 4N\ \mu_0$$



Derived allele frequency spectrum

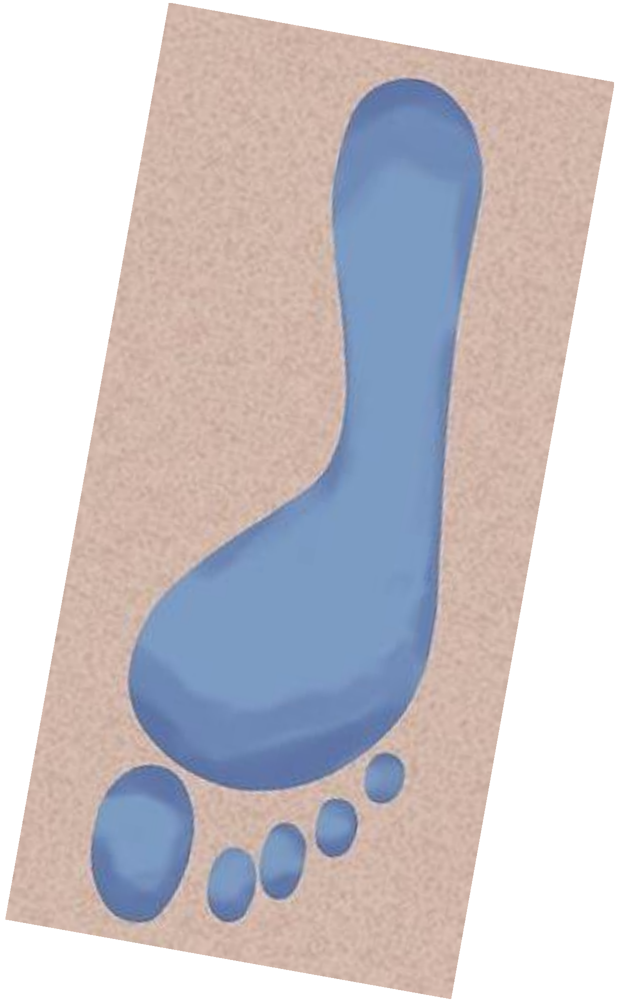
$$x(i) = \Theta\ 1/i$$

Neutral, nearly-neutral and selective domains

$$|N_e\ s|$$

Antonio Barbadilla

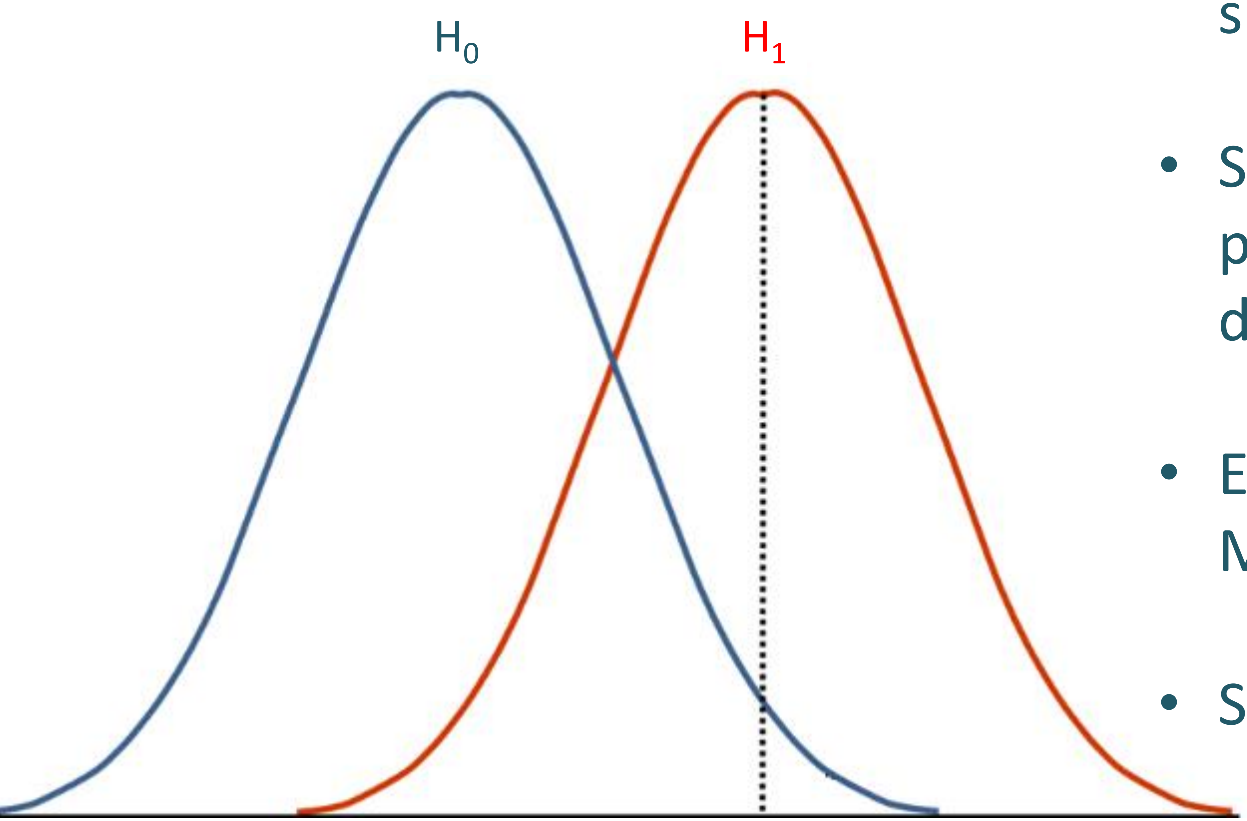
The neutral paradigm **play the role of universal null hypothesis**



Methods for the detection of selection at the DNA level: searching for the footprint of natural selection on the pattern of genetic variation

H_0: Neutral prediction

H_1: Rejection neutral prediction



Types of selection/neutral tests

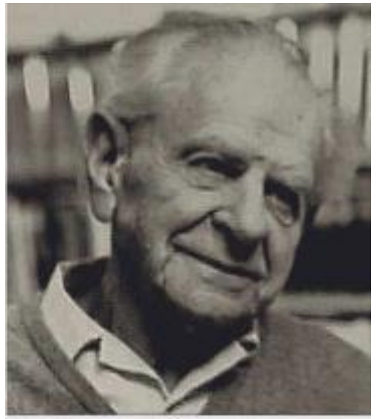
- Selection tests based on the allele frequency spectrum and/or levels of variability
- Selection tests based on comparisons of polymorphism and/or divergence between different classes of mutation
- Estimators derived from extensions of the McDonald and Kreitman test or the DFE
- Selection tests based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

$K = \mu_0$

The neutral paradigm **play the role of universal null hypothesis**

Falsifiability criterion

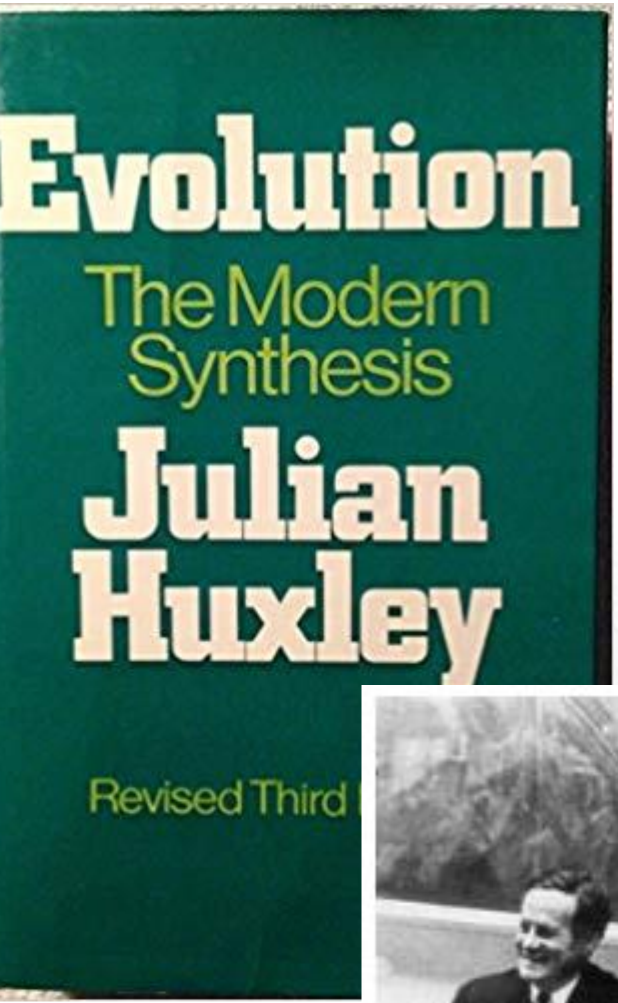
Sir Karl Popper

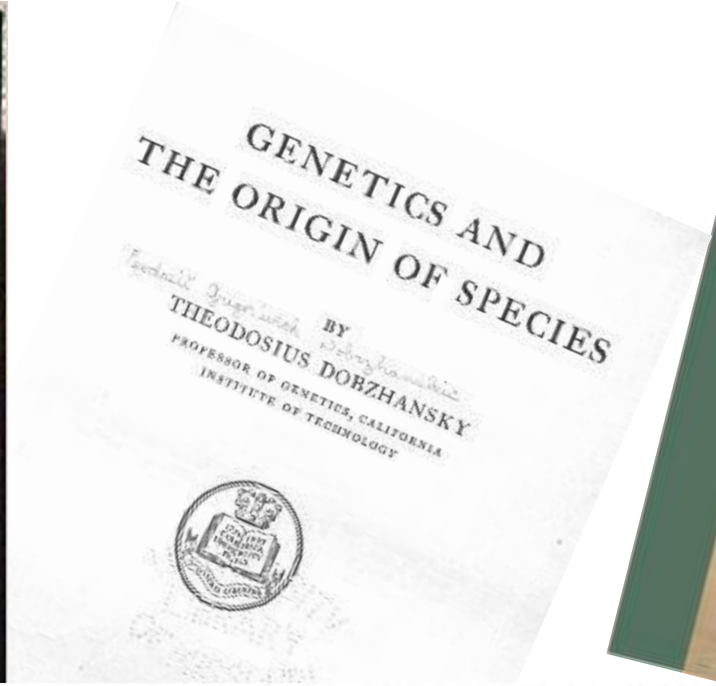


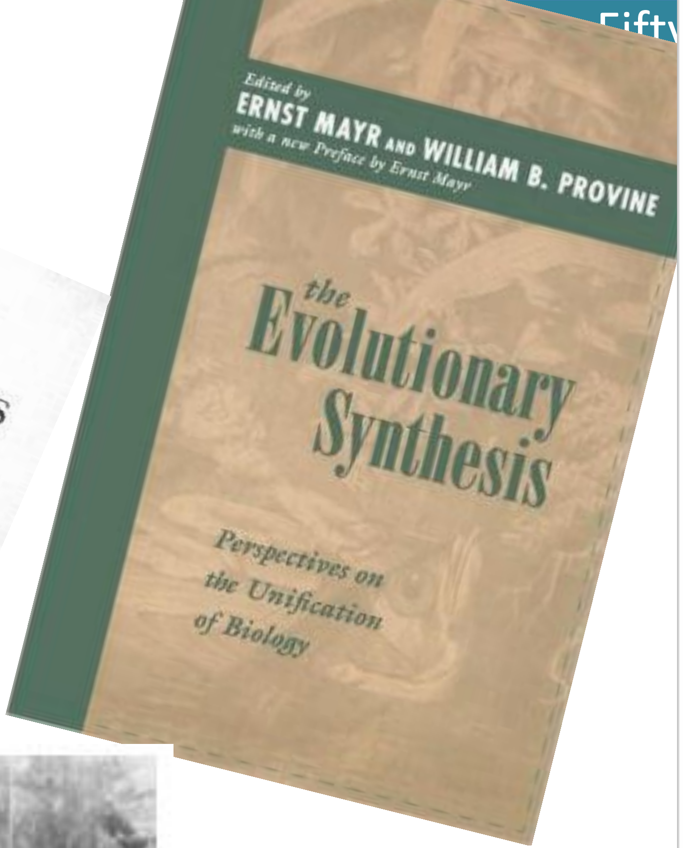
Sir Karl Popper (1902-1994)

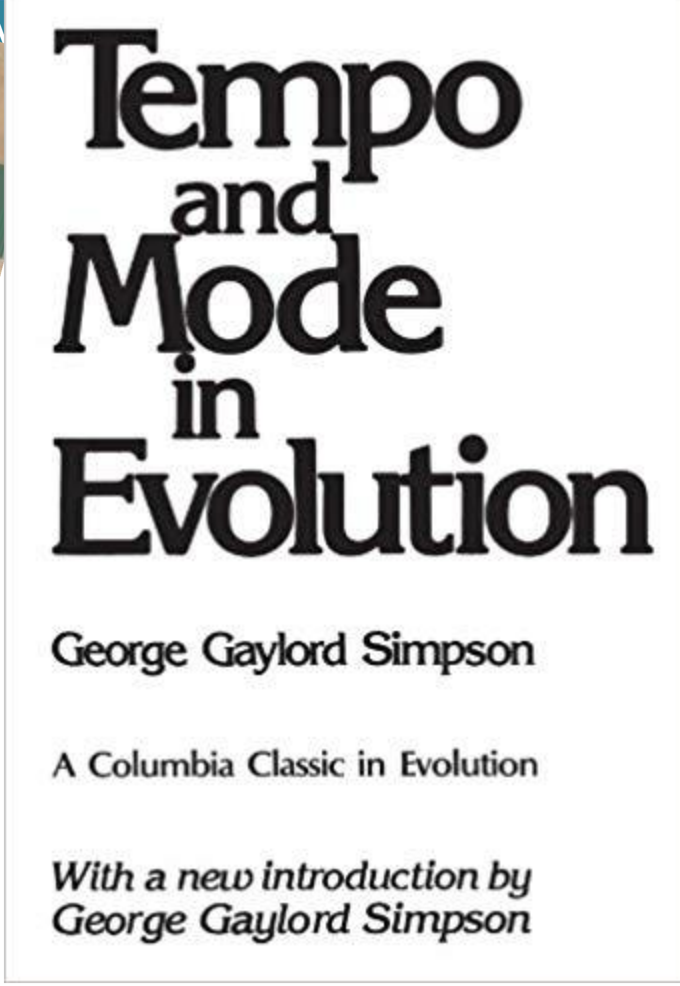
Distinctive features of Neutral Theory

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



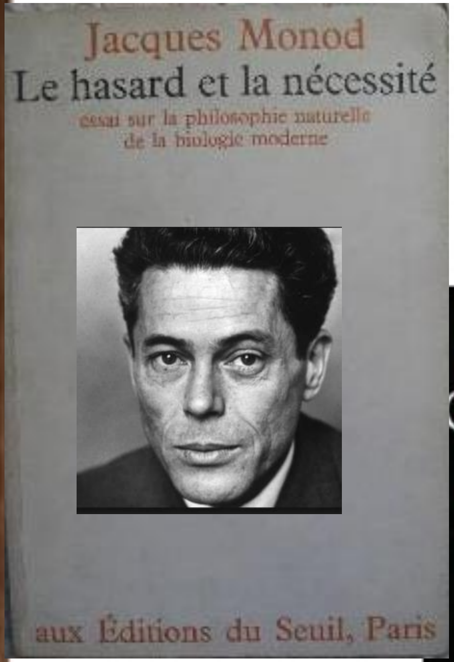


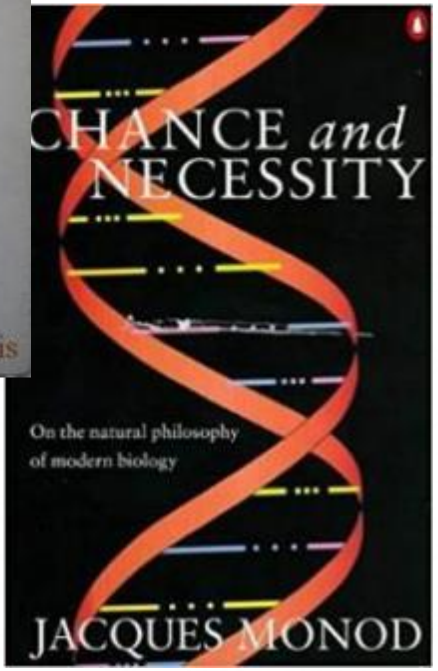




The Modern Synthesis

Role of chance in evolution





1970

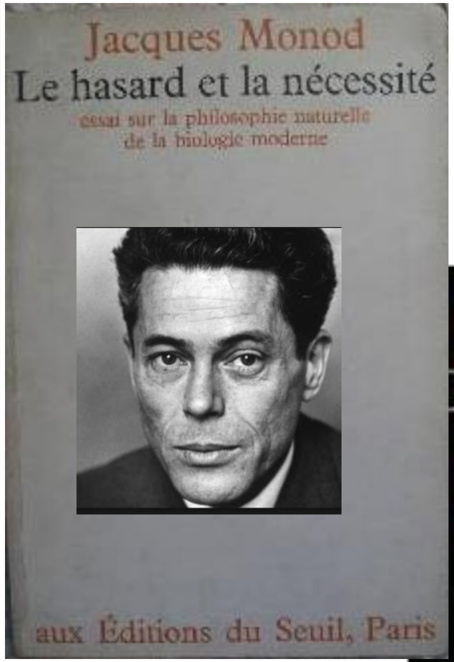
Mutation

and

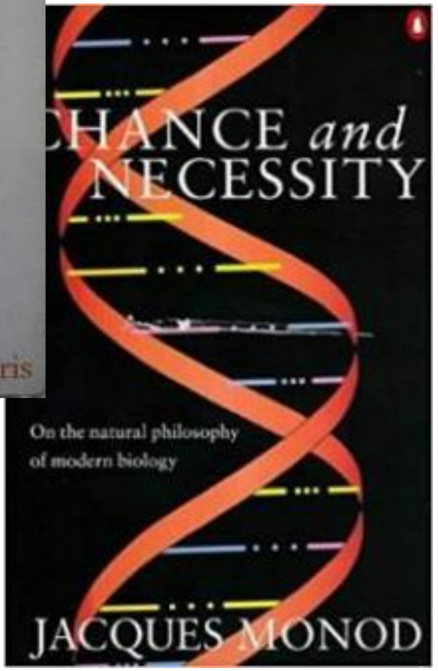
Selection

Survival of the fittest

Role of chance in evolution



Mutation
and
Selection



1970

2nd factor of chance

Genetic drift:

Random sampling of
genes in finite populations

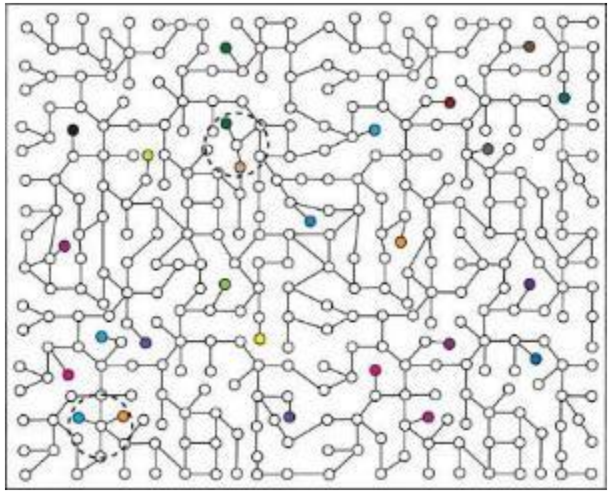
Survival of the fittest

Survival of the luckiest

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



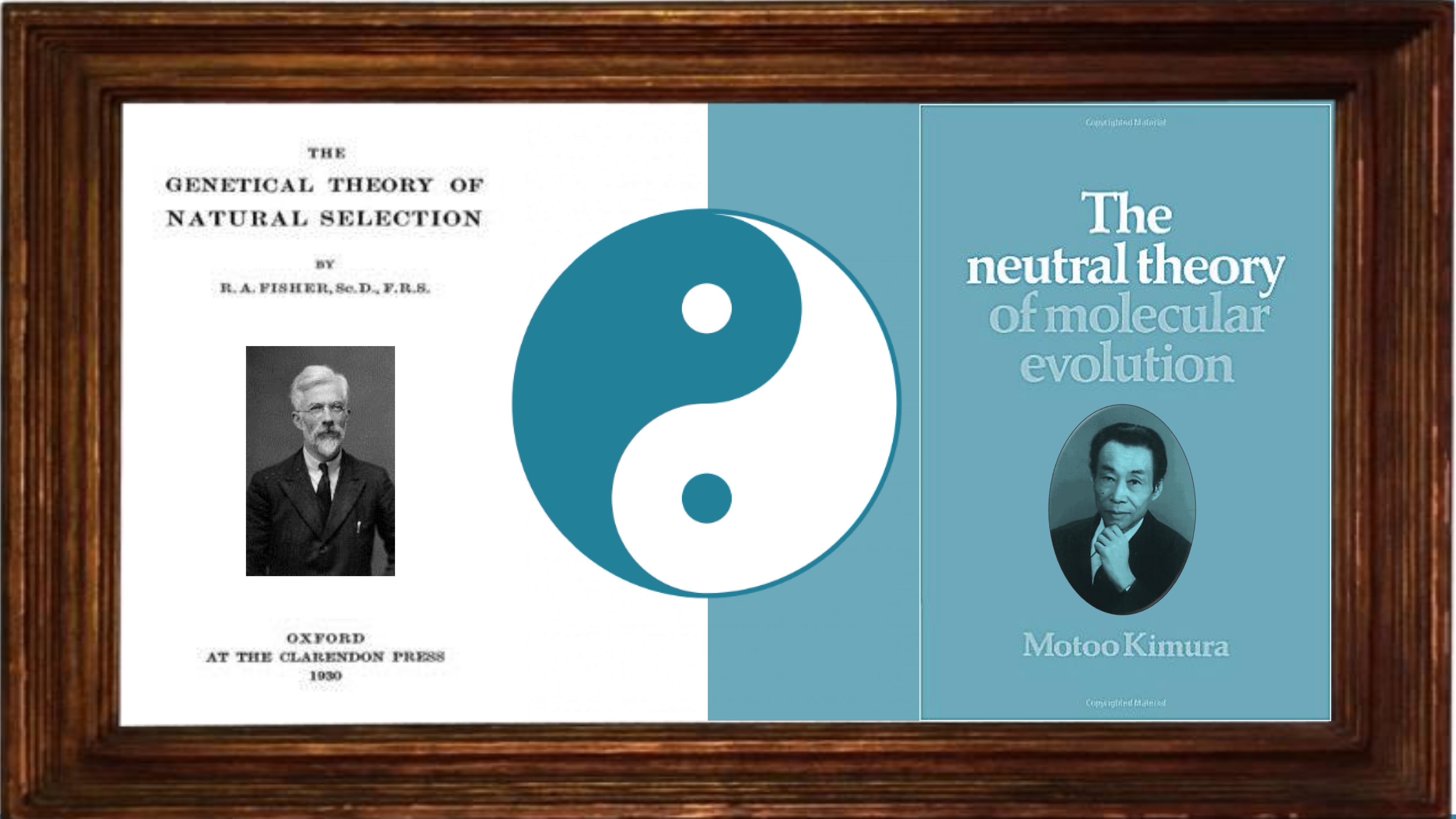
- Latent potential for selection (Dykhuizen-Hartl effect)

- Drift barrier theory (Genome complexity, M. Lynch 2007)

- Neutral gene networks (Robustness and Evolvability, A. Wagner 2008)

Lynch, Michael (2007). *The origins of genome architecture*. Sunderland: Sinauer Associates.

Wagner A (2008) Neutralism and selectionism: A network-based reconciliation. Nature Reviews Genetics 9:965-974


THE
GENETICAL THEORY OF
NATURAL SELECTION
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R. A. FISHER, Sc.D., F.R.S.
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AT THE CLARENDON PRESS
1930
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The
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of molecular
evolution
Motoo Kimura
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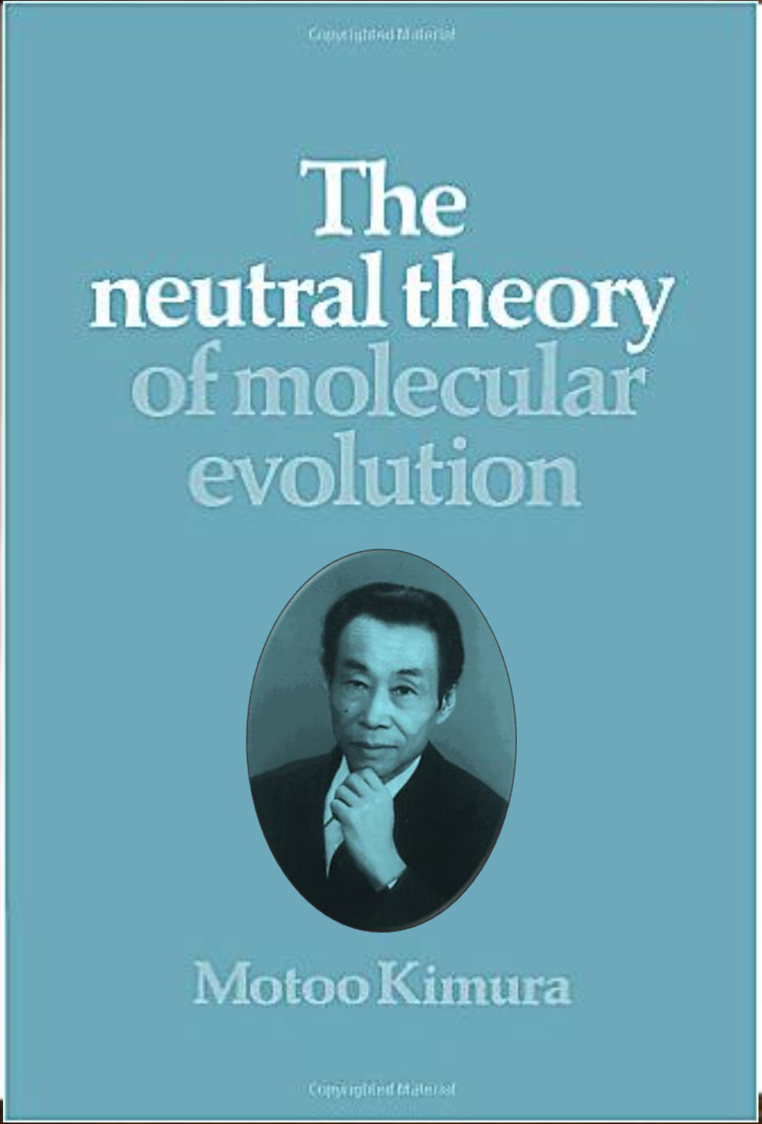
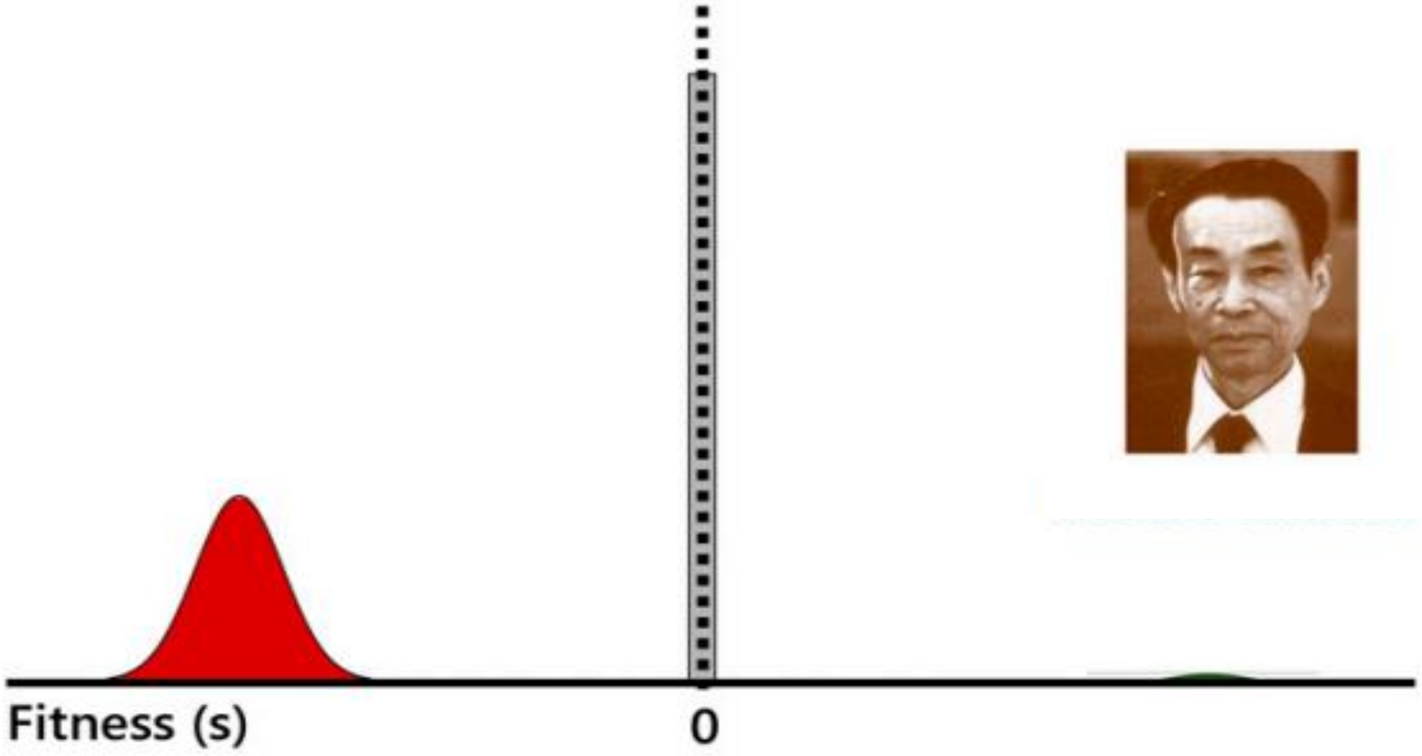


Challenges to Neutral Theory?

Neutral Theory of Molecular Evolution (1968)

Assumption

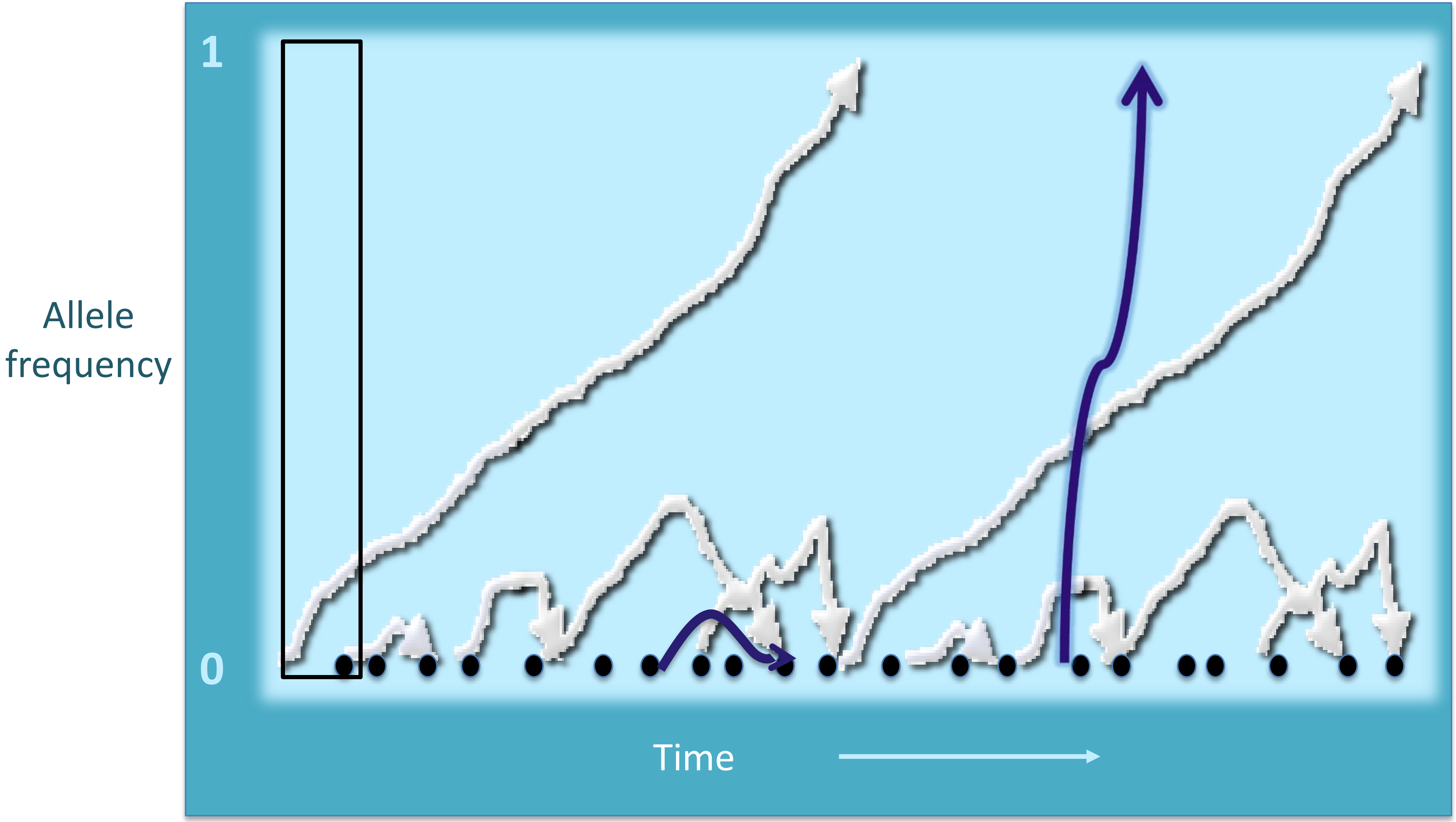
New mutations are mainly ***neutral*** *or* ***strongly deleterious***



DFE (Distribution fitness effect of new mutation) of Kimura's Neutral Theory

$K = \mu_0$

Population Dynamics of new mutations according the neutral paradigm

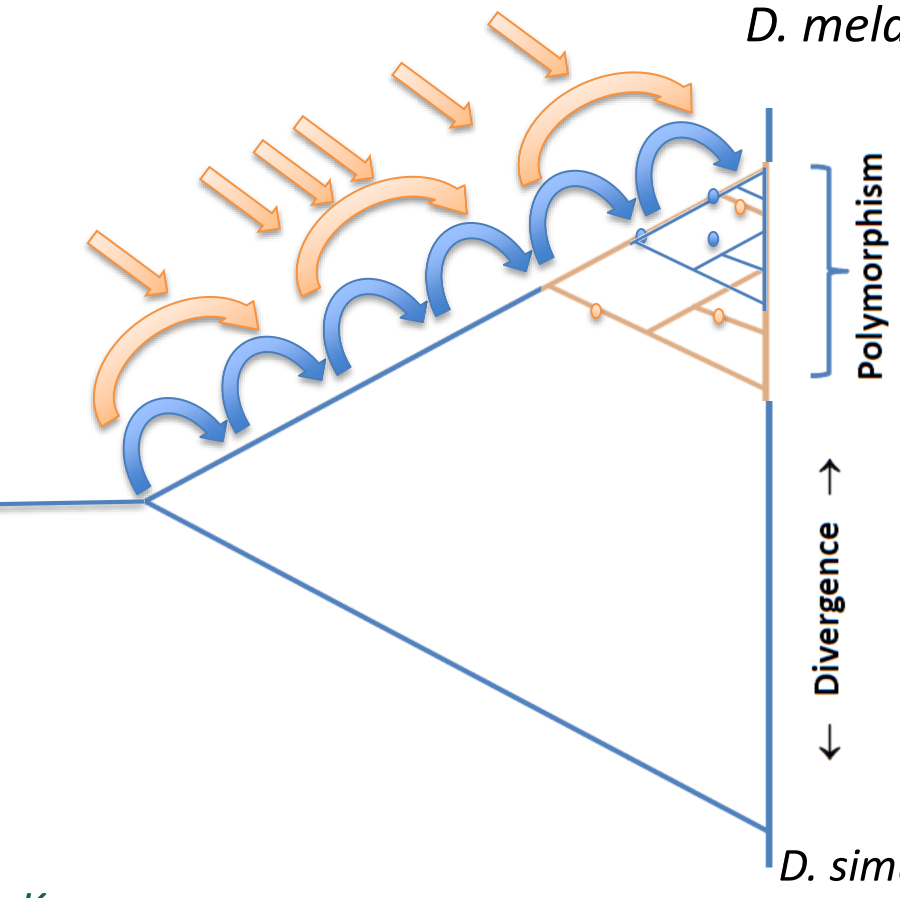


Selective variants do not contribute much to the polymorphism because of their ephemeral life at this stage

$K = \mu_0$

Maps of Genome Selection in the *D. melanogaster*

Pervasive - Rampant – Ubiquitous



- •Andolfatto P., 2005 Adaptive evolution of non-coding DNA in Drosophila. Nature **437**: 1149–1152.
- • Sella G, Petrov DA, Przeworski M, Andolfatto P (2009) Pervasive natural selection in the Drosophila genome? PLoS Genet. 2009 Jun;5(6):e1000495.
- •Mackay T. F. C., Richards S., Stone E. A., Barbadilla A., Ayroles J. F., et al., 2012 The Drosophila melanogaster Genetic Reference Panel. Nature 482: 173–178.
- •Langley C. H., Stevens K., Cardeno C., Lee Y. C. G., Schrider D. R., *et al.*, 2012 Genomic variation in natural populations of Drosophila melanogaster. Genetics **192**: 533–598.

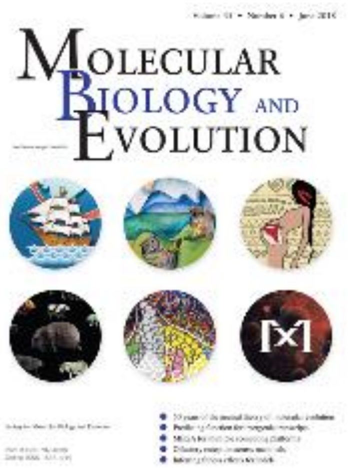
Around 30-50% of divergent amino acids are driven to fixation by positive selection

$K = \mu_0$

Antonio Barbadilla

The **hitch-hiking hypothesis** (recurrent linked selection)

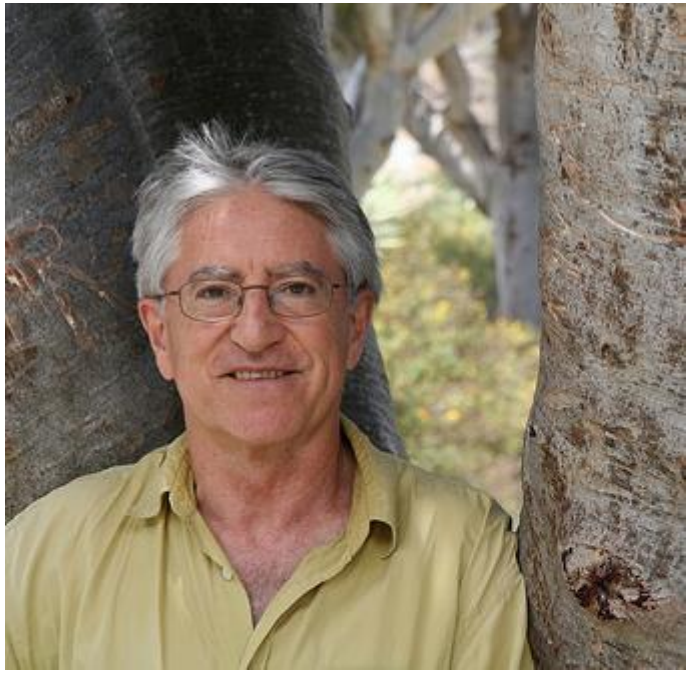
Recurrent Linked Selection: the **big challenge** to the Neutral paradigm



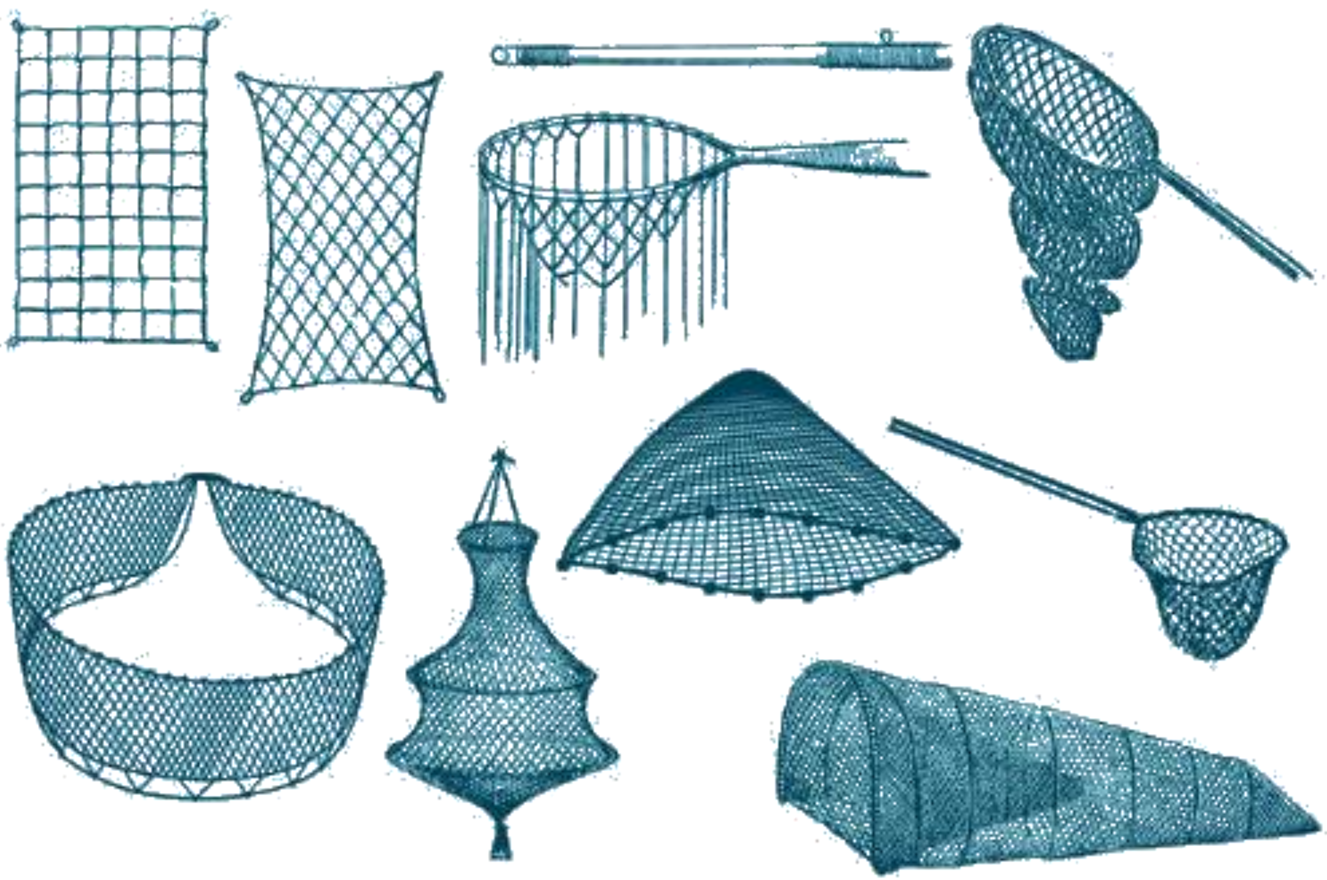
On the 50th anniversary of the neutral theory of molecular evolution, we have been charged with the task of asking: how has the neutral theory fared in light of adaptive variation within and between species? In a word, poorly.


Matthew W Hahn

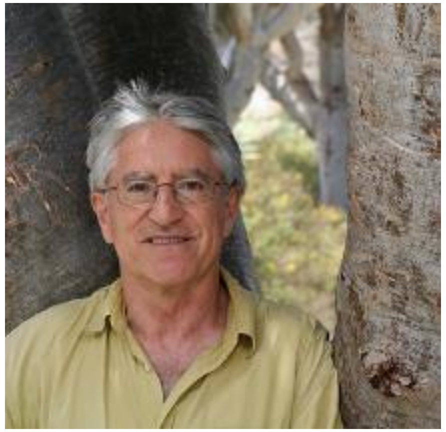
Andrew D Kern Matthew W Hahn 2018. The Neutral Theory in Light of Natural Selection. Molecular Biology and Evolution, Volume 35, Issue 6, 1 June 2018, Pages 1366–1371, https://doi.org/10.1093/molbev/msy092



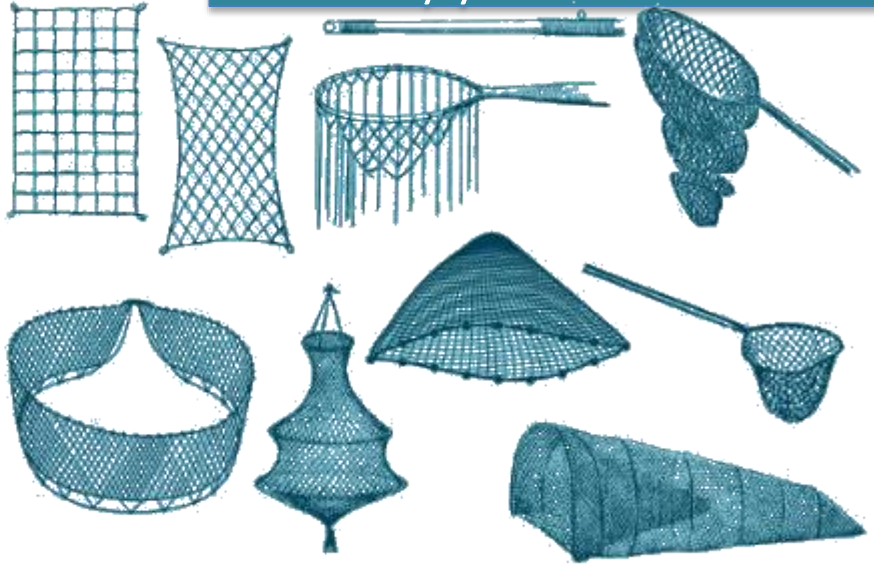
Jesús Mosterín (1941-2017)



La estructura de los conceptos y las **teorías** científicas funcionan como **redes** conceptuales



Jesús Mosterín (1941-2017)



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.

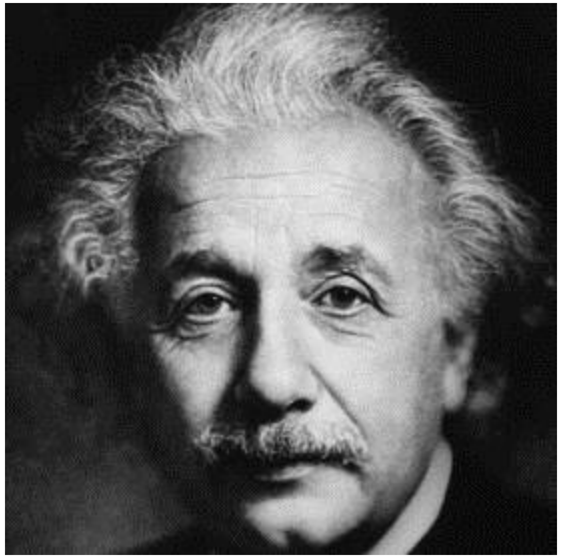
Cap. 11 Sobre teorías físicas y teorías matemáticas

MOSTERÍN, J. 2003. Conceptos y teorías de la ciencia. Alianza Editorial, Madrid.

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, rapidily evolving viral pathogens such HIV

What is Neutral Theory?

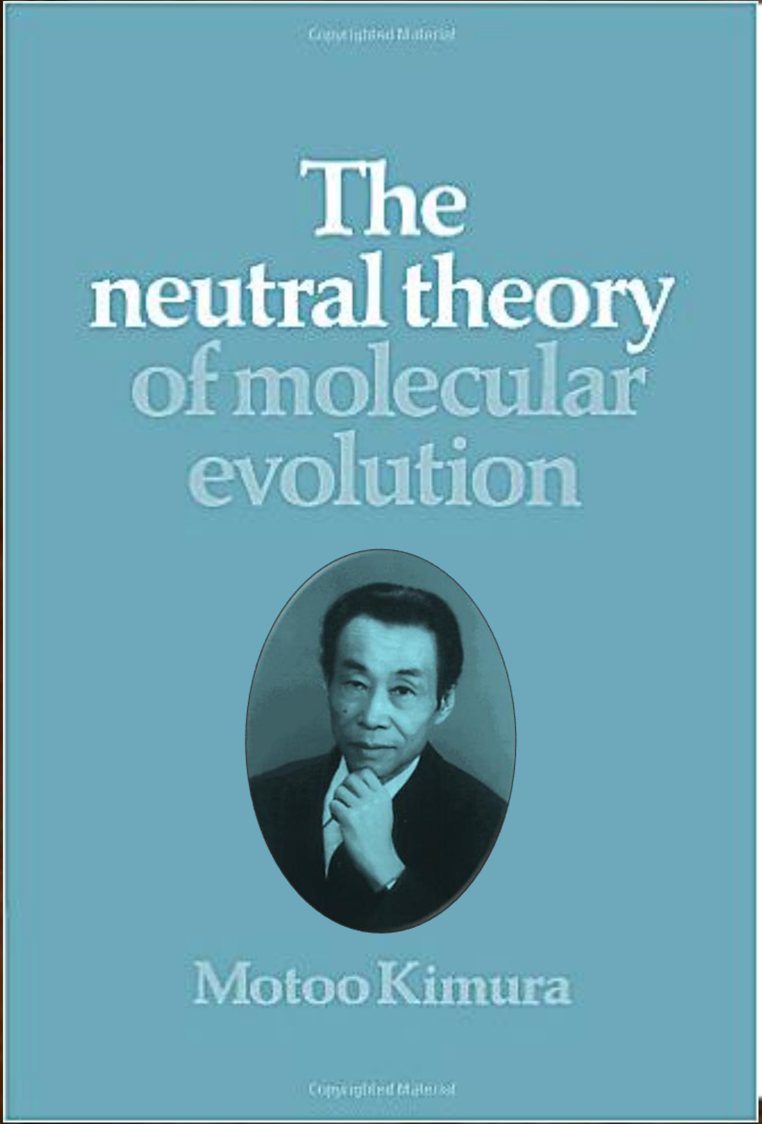


$$K = \mu \qquad\qquad E = mc^2$$

What is Neutral Theory?

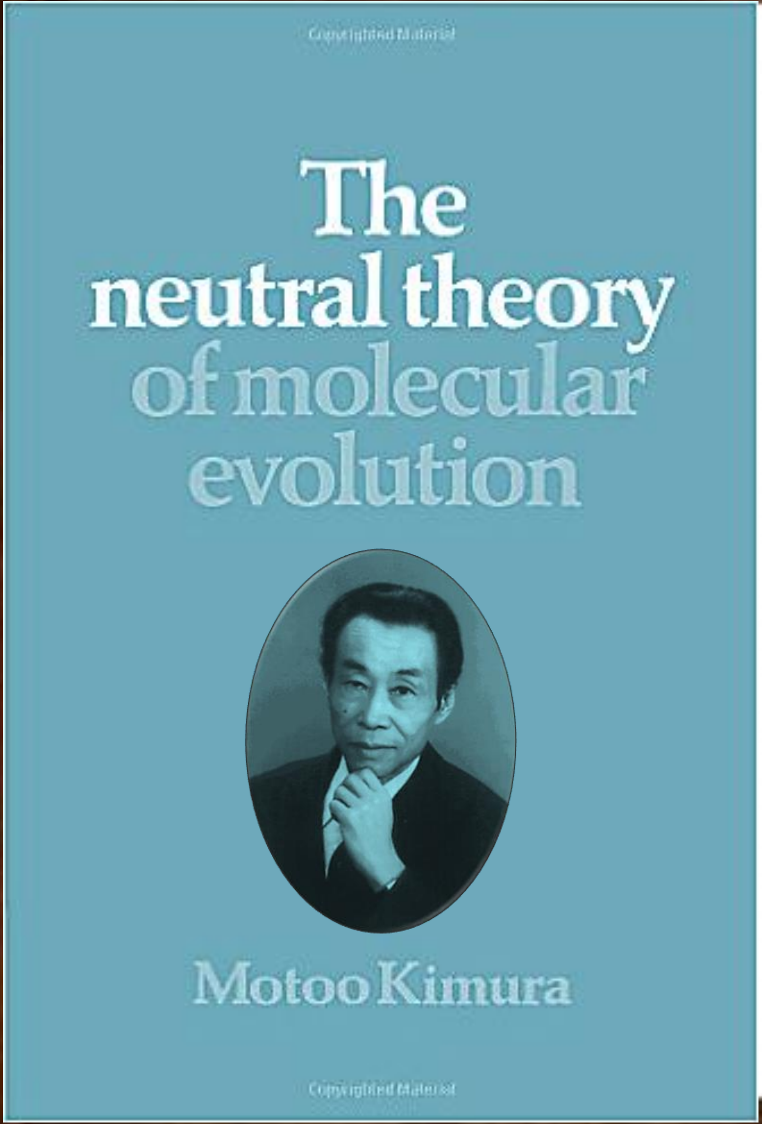
- One of the most beautiful and elegant theories of science
- An extraordinary achievement of the human intellect
- A privileged conceptual perspective to understand how chance (mutation and genetic drift) and necessity (natural selection) account for biological evolution and adaptation

Final sentence Kimura's book (1983)



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

Final sentence Kimura’s book (1983)



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

$K = \mu_0$