

“Neutralism”  
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In 1968, Motoo Kimura submitted a note to *Nature* entitled “Evolutionary Rate at the Molecular Level,” in which he proposed what has since become known as the neutral theory of molecular evolution. This is the view that the majority of evolutionary changes at the molecular level are caused by random drift of selectively neutral or nearly neutral alleles. Kimura was not proposing that random drift explains all evolutionary change. He does not challenge the view that natural selection explains adaptive evolution, or, that the vertebrate eye or the tetrapod limb are products of natural selection. Rather, his objection is to “panselectionism’s intrusion into the realm of molecular evolutionary studies”. According to Kimura, most changes at the *molecular level* from one generation to the next do not affect the fitness of organisms possessing them. King and Jukes (1969) published an article defending the same view in *Science*, with the radical title, “Non-Darwinian Evolution,” at which point, “the fat was in the fire” (Crow, 1985b).

The neutral theory was one of the most controversial theories in biology in the late twentieth century. On the one hand, the reaction of many biologists was extremely skeptical; how could evolution be “non-Darwinian”? Many biologists claimed that a “non-Darwinian” theory of evolution was simply a contradiction in terms. On the other hand, some molecular biologists accepted without question that many changes at the molecular level from one generation to the next were neutral. Indeed, when King and

Jukes' paper was first submitted, it was rejected on the grounds that one reviewer claimed it was obviously false, and the other claimed that it was obviously true (Jukes, 1991).

Why were some biologists so skeptical and others so nonchalant about the neutral theory? Why was the neutral theory so controversial? What evidence and argument was originally offered on behalf of the theory? How are tests of the theory carried out, and have any of them been decisive? Finally, what is meant by the claim that "drift" operates at the molecular level, independently of change in frequency of phenotypic traits from one generation to the next? What is "drift" in the context of the neutral theory, and how, if at all, is it distinct from drift operating at higher levels in evolution? What are the implications of neutrality at the molecular level, if any, for debates over the prevalence and explanation of adaptation? This short essay will address the above questions.

## **1. The Neutral Theory: Some Historical Background**

What it means to be "neutralist" has changed over the course of the history of evolutionary biology. An uncontroversial sense of "neutralism" is the claim that many *phenotypic* traits have no effect on an organism's fitness. The organism's *phenotype* consists of its physical and behavioral characters or traits – from height to color of plumage. Clearly, not all phenotypic traits have an impact on an organism's capacity to survive or reproduce. Darwin took note of this fact in the sixth edition of the *Origin*:

I am inclined to suspect that we see, at least in some [cases], variations which are of no service to the species, and which consequently have not been seized on and rendered definite by natural selection. Variations neither useful nor injurious would not be affected by natural selection, and would be left either a fluctuating element, as perhaps we see in certain polymorphic species, or would ultimately become fixed... We may easily err in attributing importance to

characters, and in believing that they have been developed through natural selection; ... many structures are now of no direct use to their possessors, and may never have been much use to their progenitors. (Darwin, 1872)

While it is uncontroversial that there are some phenotypic traits that have no effects on fitness, there has been considerable controversy in the history of evolutionary biology over what *proportion* of phenotypic traits were subject to selection. In other words, there has been a long controversy over whether, and to what extent, chance and accident has played a role in the distribution of phenotypic traits in populations. In the early twentieth century, there were some who thought that many if not most traits were a product of chance, not selection. Gulick (1888), and later, Wright (1931) argued that many traits differentiating local populations (polymorphisms) may be due to drift, or random fixation of traits independent of their selective value. While they argued that selection surely played a role in the differentiation and adaptation of species, they claimed that many polymorphic traits may have simply been a by-product of isolation and sampling error, or, the random sampling of certain types of individuals versus other types from one generation to the next (See, Provine, 1986 for a discussion). In the 1930's and 40's, many biologists accepted the view that quite a few phenotypic traits were due to drift. In the 1950's and 60's however, there was somewhat of a sea change in favor of selectionist views. In part, this was because of the discovery that some phenotypic traits formerly regarded as neutral were in fact selected for (blood groups). (See Crow, 1985, for a discussion).

While most evolutionists were more or less pan-selectionists<sup>1</sup> in the 1950's and 60's, there was some controversy over what to expect at the genetic level, if indeed,

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<sup>1</sup> "Pan-selectionism" is the view that all or almost all traits were at some point shaped by natural selection.

selection was the major factor in phenotypic evolution. At one extreme, proponents of what Dobzhansky coined the “classical view,” held that the relentless action of selection should make the genetic material relatively uniform, or homozygous. Deleterious mutations are regularly eliminated, proponents of this view maintained, and occasionally, favorable mutations arise that are eventually incorporated into the population. At the other extreme, the “balance” theorists suggested that genetic polymorphisms might be held in “balance” by selection (For a discussion of this debate, see Dietrich, 1994). In other words, it was not obvious in the 1960s, even if selection was the major factor at work in evolving populations, whether the genetic material should as a result be uniform, or how uniform it should be.

“Neutralism,” in Kimura’s sense, is distinct from both senses mentioned above; i.e., he was not concerned with whether or to what extent, phenotypic evolution was neutral, or whether, assuming selection was in operation, the corresponding genetic material should be heterozygous or homozygous. Rather, he was concerned with a different “level” at which evolution is going on – the molecular level. According to Kimura, “Neutralists claim that the amino acid and nucleotide changes that accumulate within the species in the course of evolution are mainly due to random fixation of selectively neutral mutants”(p. 152, Kimura, “Discussion Forum: Molecular Evolution,” *TIBS*, July 1976). Kimura’s paper was brief and elegant. The argument was as follows. First, Kimura reports on the rate of amino-acid substitution in hemoglobin, triosephosphate dehydrogenase, and cytochrome c in mammals. The observation that there was a constant rate of amino acid substitutions in these genes had been hailed as the “molecular evolutionary clock” – i.e., the rate of change in these sequences could be used

as a “clock” to estimate times to most recent common ancestor in species sharing these genes (Zuckerlandl & Pauling, 1965). Second he extrapolates that rate to the entirety of the genome. Third, he concludes that nucleotide substitution in the history of mammals has been so fast that it is on the order of one nucleotide pair “roughly every 2 yr.” The crux of his argument is as follows: this rate is simply too high to be consistent with Haldane’s “cost of selection,” or, in Kimura’s words, “substitutional load.”<sup>2</sup> Thus, these changes must be effectively neutral.

Kimura also gave a very elegant mathematical argument, demonstrating that if the neutral theory was true, the rate of change in the genetic constitution of a population should be exactly proportional to the mutation rate, and independent of population size. In a diploid species containing  $2N$  alleles, the probability that an allele will become fixed is  $1/2N$ . If the mutation rate per generation is  $u$ , then  $2Nu$  represents the number of new mutants introduced into the population each generation. Thus, if there is no selection, the rate at which new mutations become fixed in a population should be equal to  $(2Nu)(1/2N)$ , which is equal to  $u$ . That is, the rate of change at the molecular level should be constant over time, directly proportional to mutation rate, and independent of population size.

## **2. Reception of the Theory:**

When Kimura first proposed his theory, James Crow writes that: "The initial response was generally one of dismay and disbelief. The reactions ranged from

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<sup>2</sup> The cost of selection is the selective death that must occur for a gene to be substituted (Haldane, 1957). For further discussion, see below.

skepticism to outright rejection. To some it was utter nonsense."(See James Crow, 1985a, p. 1.)

On the other hand, Ford Doolittle reports,

I was a graduate student in the 1960's, but I was a molecular biologist, so the neutral theory struck me as "duh." Because we were used to looking at lots of sequences and saying, "These are the important residues. They must be functional. These others must not matter." So even though I was in Charlie Yanofsky's lab, and he was a panadaptationist—at least at some level—at the same time we could entertain the fact that these amino acid changes that you could see in the spectrum of sequences were neutral. We always said, "What are you guys so excited about, because it's just obvious." (MIT Website in History of Science and Technology, [http://hrst.mit.edu/hrs/evolution/public/transcripts/ideology\\_transcript.html](http://hrst.mit.edu/hrs/evolution/public/transcripts/ideology_transcript.html))

Thus, there were two extreme responses. On the one hand, some rejected Kimura's arguments. On the other, some regarded his results as obvious. What explains this divide? First, why did the neutral theory strike molecular biologists such as Doolittle as so commonsensical?

Long before the neutral theory was proposed, biochemists and molecular biologists were aware that enzymes – proteins, which are composed of long chains of amino acids with a characteristic shape and function, that assist chemical reactions in the cell – have an “active” site combined with a substrate. The active site is the area of the molecule that contributes to the function of the enzyme in the cell, such as breaking down or transporting other molecules. The functional sites of many important enzymes – e.g. cytochrome c – are uniform among vertebrates. However, what Sueoka (1961) called “dispensable” parts of the molecule, vary across vertebrates. In the 1960s, molecular biologists Margoliash (1963), Zuckerkandl and Pauling (1965) found that the non-functional parts of enzymes evolve in a regular, clock-like fashion, without

compromising the enzyme's function in the cell. As early as 1966, Thomas Jukes commented on these observations:

If we consider as an example the two cytochrome c molecules found respectively in dogs and horses, it will be noted that these differ in about 10 of the amino acids in a chain of 104. The question arises, are the two molecules splendidly tailored to the different requirements specified by "dogfulness" and "horsefulness," have they evolved to conform to these different requirements, or have the two cytochromes been carried along as dogs and horses evolved separately from a common ancestor? ... It is undoubtedly quite probable that separation of the two species would be followed by changes in the genes that in time would result in differences in the two cytochrome c molecules. (Jukes, 1966 *Molecules and Evolution*: New York: Colombia University Press, (in Jukes, "Early Development of the Neutral Theory," 1997, p. 474))

So, the fact that many parts of molecules – even some that have a hugely significant function – have "dispensable" as well as functional components, made the neutral theory seem, not only initially plausible to many biochemists, but obvious.

However, the neutral theory was not so obvious to many evolutionists. Even if many changes at the molecular level might be functionally neutral, many biologists were skeptical that all or nearly all genetic variation could have little or no effect on an organism's phenotype. They found the arguments Kimura offered on behalf of this claim unpersuasive.

### **3. Kimura's Arguments for Neutral Evolution**

What was the reasoning in favor of this claim? Recall that Kimura claimed that there were too many genetic substitutions for selection to be the primary factor in evolutionary change at the molecular level. He claimed that the "cost of selection" or "mutational load" would be too high. What is the "cost of selection" and why would it be too high? The cost of selection is the selective death that must occur for a gene to be

substituted (Haldane, 1957). Selection causes a certain number of individuals to die in each generation. So, selection imposes a “cost” on the remaining (fitter) members of the population to reproduce at a higher rate to make up the difference. If the remaining members of the population do not reproduce enough to make up the difference, then the population will go into decline. If this goes on long enough, the population could be driven to such low levels that it will become extinct.

As the proportion of individuals carrying the less fit alleles in the population decreases, the cost of selection will also decrease. In other words, as there are fewer and fewer suboptimal individuals in a population, the lower the load on the population will be. So, a “selectionist” – i.e., someone who thinks that most of a population is of high fitness, or very close to an adaptive peak – will think that the load cannot be very high. Many evolutionists took this to imply that if selection was, as Darwin said, constantly “scrutinizing” every trait, then the genetic material should be relatively uniform. The cost of selection will thus place an upper limit on the rate of evolution. The upper limit suggested by Haldane for a diploid population was one gene substitution per 300 generations. Haldane’s cost of selection was used to argue that the rates of molecular evolution are too fast to be explained by natural selection.

#### **4. Tests of the Neutral Theory:**

In order to test the neutral theory of molecular evolution, we have to know what it would look like if most of the variation at the molecular level was indeed due to drift, or random fixation of alleles, rather than selection. What would the “signal” of randomness be? Part of the history of the debate over the neutral theory has been over exactly this



question; what should we expect if Kimura is correct? Until relatively recently, almost all of the tests of the neutral theory either had little statistical power, (in other words, they could not rule out selection), or were indecisive. Before the 1980's, tests of the neutral theory were conducted viz. examination of protein polymorphisms, or variations detectable with electrophoretic data. In the 1980s and 90s, DNA sequence data became available, and molecular biologists did indeed find a great deal of variation at the genetic level. However, there is variation and there is variation. "Fixed differences" or "divergences" are genetic differences between species; for instance, if one species has nucleotide A at a certain site and another has nucleotide G. In contrast, "polymorphism" is nucleotide variation that distinguishes two alleles within a species. If the neutral theory is true, both types of variation should evolve at the same rate – in other words, the neutral mutation rate should explain both polymorphism within and between species. However, we cannot observe and compare these rates directly; rather, we must examine present patterns of fixed differences and polymorphism and infer backward as to their causes.

Testing the neutral theory is enormously difficult, exactly because there is the difficult problem of differentiating genetic variation that is due to selection from variation that has no effect on fitness. Martin Kreitman nicely sums up the dilemma of searching for signals of selection versus drift as follows:

The detection of positive selection in DNA sequences poses an immense challenge. The genetic material can be likened to a device that faithfully records every informative event (i.e. mutation) but then over time proceeds to either erase (by back mutation) or obscure (by parallel mutation) some of the recorded information. Furthermore, there is not simply one recorder playing at any one time, but a whole population of them (the gene pool), and each records a slightly different, but correlated, version of history. However, only one of these recordings or, more accurately, a heavily spliced (i.e., recombined) version gets

saved for posterity... Which spliced snippets get saved depends upon innumerable chance events, ranging from the relatively benign drift of a neutral mutation in a large population to the strong directional shifts in allele frequencies at sites linked to an adaptive mutation. So, even though every functionally important mutational event in the history of a species, is, by definition, recorded in the DNA sequence of a species, these informative mutations are likely to be embedded in a sea of less meaningful ones (selectively neutral and nearly neutral mutations) and are likely to be associated with stochastic events that can result in many possible configurations of linked variation or change. The challenge of detecting selection at the level of DNA is the challenge of finding its signal in a leaky, lossy medium. (p. 540, Kreitman, 2000)

So, how do biologists meet such a challenge? There are at least twelve different tests of selection at the DNA level (For a Review, see Kreitman, 2000). The current state of the field is in flux; new tests are being developed all the time, and claims to have demonstrated the neutral theory over the past twenty years have been closely followed by claims to the contrary. All tests of selection at the DNA level are not tests of the neutral theory, per se. Rather, they assume neutrality, or use the neutral theory as a “null hypothesis,” and look for departures from neutrally evolving sites. There have been many cases found of signals of “selection” at the molecular level. However, this does not count as a refutation of the neutral theory. There is no question that some parts of the genome have been strongly constrained by selection, and other parts are not so constrained. In other words, today, the question of whether the neutral theory is correct is not an “either-or” question, (whether there is neutral evolution), but a “more-or-less” question, (that is, what proportion of evolution at the molecular level is neutral).

One example of a very popular test of the neutral theory is the MacDonal-Kreitman, or MK test. The MK test, (or, rather, the family of tests, as there are several versions), compares the ratio of variability in “replacement” and “synonymous” sites. The DNA code is “degenerate”, which means that not all changes in the nucleotide

sequence entail changes in the amino acid and protein produced by that sequence. Thus, “replacement” sites are sites where changes the nucleotide sequence will change the amino acid sequence of a protein. “Synonymous” sites are sites where changes in the sequence do not change the amino acid sequence of a protein. If the bulk of molecular evolution is neutral, then the variability within a species and the rate of evolution between species are each linearly related to the neutral mutation rate. The MK test compares the number of fixed differences for replacement and silent nucleotide changes, dividing one by another to get a ratio. Then, this is compared with the ratio of polymorphism within species for replacement and silent sites. The two ratios should be equal if all changes are neutral. If the ratios are significantly different, however, then one can predict with some confidence that selection has acted to change the amino acid sequence for some protein.

## **5. Neutralism & Adaptive Evolution: The Molecular and the Phenotypic Level**

What are the implications of these tests? If we discover that many if not all change at the molecular level is neutral, what are the implications for adaptive evolution? Does this mean that many if not most phenotypic traits are not products of selection? The answer is no. It may well be the case that most if not all evolution at one level is neutral, and that at another level, it is strongly controlled by selection. This may seem like a paradox, but it is not. Phenotypic traits are controlled by many genes, and, there is a good deal of “redundancy” in both the genetic and developmental bases of selectively significant phenotypic traits. In other words, there might be a good deal of “give”

between the genetic bases of certain traits and their phenotypic expression. Thus, it may well be the case that most if not all of evolution at the molecular level is due to drift, and at the same time, most if not all evolution at the phenotypic level is a product of natural selection.

Thus, that most traits are controlled by “drift” at the molecular level is not the same as to suggest that random chance and accident has controlled the fixation of most phenotypic traits in evolution. There is a sense in which what happens at the molecular level is relatively independent from that at the phenotypic level. Drift in the classical sense was assumed to operate on discrete genes that controlled discrete phenotypic traits. On the classical model of drift, the main “cause” of drift is change in effective population size; intuitively, this makes sense, as when populations are drastically reduced in size, by chance alone, there will be a radical shift in the distribution of traits in that population.

The classical “Wright-Fisher” model represents drift by random binomial sampling.<sup>3</sup> In other words, we take generations to be discrete, and imagine that alleles (where there are two alleles at a gene locus) are “sampled” from one generation to the next, in the way that balls are drawn from an urn (we are to assume that phenotypic traits are closely associated with specific alleles). So, for instance, consider two individuals in

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<sup>3</sup> There are several problems with this model of drift. First, Mendelian independent assortment is systematically false. As Sturteyvant pointed out, one can use failure of independent assortment to map locations of genes on chromosomes. Roughly speaking, the less “independent” genes are, the more closely linked they are on a chromosome. Some (Provine, unpubl.) have argued that given the failure of independent assortment, drift in the classical sense is never instantiated. And so, in some sense, there is no such thing as drift, as no populations of organisms in nature are correctly described by the Wright-Fisher model. More worrisome still, Gillespie has pointed out that we may get the same data that we might get were a population to meet these conditions, either by a process of fluctuating selection, or draft. Draft is when genes are swept along to fixation because they are linked to genes that are strongly selected for. They are swept along, as it were, in the “draft” of a selective sweep.

This creates a whole slew of problems for testing drift v. selection. Suffice it to say that it is an idealized assumption of classical models of drift that sampling is “perfectly” random, and that testing claims about the relative significance of drift versus selection in any case is no small feat.

a parent generation, one of which is heterozygote AB and another homozygote, AA. Given the Mendelian assumption of independent assortment, these two individuals can have offspring of one of two sorts, either AA, or AB. By chance alone, they may have an equal number of AA and AB offspring, or, alternatively, ten offspring that are all AA, or ten offspring that are all AB. Summed over the population as a whole, the change in distribution of gene frequencies due to independent assortment is called drift. In other words, the “cause” of a drift in gene frequencies in this sense is simply redistribution due to independent assortment, or accidents of “sampling” of alleles. What is meant by “cause” in this context? Mendelian independent assortment is a cause of drift in the same way that the fact that automobiles have internal combustion engines is a cause of the long lines for gasoline during the 1973 Middle East oil embargo. It is a condition on the possibility of drift, insofar as drift is understood as binomial random sampling, that there be independent assortment.

It is important to distinguish conditions on the possibility of drift occurring, where drift is represented by some model, from law-like regularities about how the effects of drift can be increased or decreased. For example:

- Decreasing population size increases drift. Or, suppose you have two sets of populations and imagine that there is no selection, mutation, migration or assortative mating in such populations. Time to fixation of alleles in population of smaller size will be much less than in population of larger size. By drift, or chance alone, alleles will drift to fixation more quickly in smaller populations.

- This is true for the same reasons that one expects a smaller sample of flips of a fair coin to be skewed towards heads or tails than a larger sample.
- Patterns of mating – such as polygamous mating patterns or polyandrous mating patterns – can increase the effects of drift. Such mating patterns reduce what is called the ‘effective population size’
  - Selfing (or self-fertilization (often occurs in plants)) or assortative mating both increase the effects of drift
  - Whenever selection coefficients are smaller than  $1/2N_e$ , drift will win out. Or, the fate of alleles with such selection coefficient will be controlled largely by drift. Selection is operating, but too weak to offset the influences of chance events.
- “Effective population size” is the size of an idealized population that would have the same effect of random sampling on gene frequency as that in the actual population.

Thus, there are, on the one hand, conditions for the possibility of drift occurring, and on the other, law like general claims about how random fixation of alleles can be speeded up or slowed down.

So, there is a sense in which “chance” in evolutionary biology is subject to laws. This may seem inconsistent, it is not. On the one hand, there are robust, law-like type-level claims about drift. The problem is that we don’t always know which of these law-like ways in which the effects of drift (or, chance) can be increased or decreased is in operation. Stochastic gene frequency change will always occur, so long as the conditions mentioned above are met. And, stochasticity can be increased by population bottlenecks,

changing mating patterns, or what have you. In this sense, there are law-like explanations of how drift works, or how stochastic changes in gene frequency can be manipulated. There are nomological facts about drift.

## **6. What is Drift in the Context of the Neutral Theory?**

The classical models of drift were generated before biologists knew that genes were composed of DNA. So, what “drifted” were gene frequencies, where it was assumed that inheritance was Mendelian, and there was a direct relationship between genes and phenotypic traits. Of course, neither of these assumptions is strictly true. So, the models and the ways of thinking about the role of chance in changes of phenotypic traits in population has to be adapted to advances in genetics and molecular biology. Models of molecular evolution use the term “drift” to describe fixation due to “chance”. However, most of the models of “drift” at the molecular level treat the fixation of genes as a continuous process – specifically, they are diffusion models. In other words, they are continuous approximations of underlying discrete processes. However, the approximations are quite accurate even given this false assumption. The important difference between modeling drift at the molecular level versus the phenotypic level, however, is that, assuming the neutral theory, the rate of fixation of alleles due to drift at the molecular level is independent of population size. This marks a striking difference from classical models of drift, where effective population size is the main predictor of the extent of fixation due to drift. So, what is the “cause” of drift at the molecular level? It turns out that this is a rather difficult question to answer. While it is true that there are systematic regularities or expectations we might have about the extent of polymorphism,

or genetic heterozygosity in populations of different sizes, we cannot say that population size exactly is the “cause” of this heterozygosity. Rather, populations of larger size will tend to have a wider or more diverse samples of alleles, and so, these alleles will take a longer time to be eliminated or fixed due to random sampling, than will alleles in a smaller sample. But, the causes of these “fixation” events are, by definition, “random” – since, were there to be deterministic regularities in their fixation, they would be due to selection, not drift.

According to Woodward (2003), causal claims are essentially claims about how manipulation of one variable, (or change in the value of that variable) is capable of changing the value of a second variable. Insofar as manipulating population size can increase the effects of drift, one might speak of drift as a “cause” in Woodward’s sense of cause (Riesman and Forber (2005, forthcoming). However, what is manipulated here is population size, not drift per se. Drift is simply random sampling of alleles from one generation to the next. Reducing population size can increase the effects of random sampling; just as reducing a sample of coin flips can cause a skew of flips toward heads.

However, if Kimura is to be believed, the effects of drift at the molecular level are independent of population size. Moreover, if we take drift to always be in operation when populations are finite, drift will occur with or without manipulation of population size. Insofar as any system which meets conditions on drift described in the above section will be subject to chance, and all populations meet these conditions, it becomes analytically true that whatever change in frequency distribution one observes from one generation to the next is caused, in part, by drift, whether or not population size has been manipulated. Put differently, any and all change in distribution of gene frequencies in a



finite population must be in part due to drift. So, while it is true that changes in frequency distribution may be due to manipulations of population sizes, drift at the molecular level, at least in the case of neutral alleles, is supposed to be independent of such manipulations, and any case of shift in distribution that is not due to deterministic causes, whether population sizes have been manipulated or not, is called “drift”. It seems that there are open questions as to what exactly is being “manipulated” in the case of drift, and in what sense drift is a “cause” of evolutionary change.

To sum up: reducing population size increases variance in gene frequency distributions. Woodward has it that whatever manipulation or choice of a value for a variable  $x$  that effects a change in some value of a variable  $y$  is a cause. So, it seems his model would have it that choosing a small sample is a cause of any resulting skew in distribution of heads or tails. However, not all will agree that this sort of variable causation is the same as “actual” causation. What this debate hinges upon, it seems, is what we are willing count as variables, and whether causes must be relationships between events in space and time. What makes it the case that smoking “causes” cancer? Is it that individual smokers develop cancer, or that there is a population level probability of getting cancer if one is a smoker? What makes it the case that choosing a small sample of coin tosses causes skew in distribution? Does it have to do with the weight of the or the force of the tosses, or, with the fact that populations of tosses are finite and the law of large numbers? It seems that what we want to call the “cause” of a result depends to some extent upon where we want to pitch the explanation. If we’re interested in population level changes in distribution, we may refer to small sample size as a “cause”. But, this is not to resolve the metaphysical question of where the causes are.

## **Bibliography:**

- Crow, 1985. "Motoo Kimura: An Appreciation," in *Population Genetics and Molecular Evolution*, eds. T. Ohta and K. Aoki. Tokyo: Japan Scientific Societies Press.
- 1985. "Neutrality-Selection Controversy." In Kimura and Ohta, *Population Genetics and Molecular Evolution*. Japan Scientific Societies Press: Tokyo. Springer Verlag: Berlin. Pp. 1-18.
- Darwin 1872. *Origin of Species*. 6<sup>th</sup> ed. Murray, London.
- Dietrich, 1994. "The Origins of the Neutral Theory of Molecular Evolution." *Journal of the History of Biology*. 27: no. 1 pp. 21-59.
- Dobzhansky, 1955. "A Review of Some Fundamental Concepts and Problems in Populations Genetics," *Cold Spring Harbor Symposium in Quantitative Biology*, 20.
- Gulick. 1888. *J. Linn. Soc. London*. 20: 189-274.
- Haldane, 1957. "The cost of natural selection" *J. Genetics* 55: 511-524.
- Jukes, 1991. "Early Development of the Neutral Theory." *Perspectives in Biology and Medicine* 14 473-485.
- Kimura, 1968. "Evolutionary rate at the molecular level." *Nature*. 217: 624-626.
- Kimura, 1976. "Discussion Forum: Molecular Evolution," TIBS, July.
- King and Jukes, 1969. "Non-Darwinian Evolution" *Science*. 164: 788-798.

Kreitman, 2000. "Methods to Detect Selection in Populations with Applications to the Human," *Annual Review of Genomics and Human Genetics* 1: 539-569.

MIT Website in History of Science and Technology,

[http://hrst.mit.edu/hrs/evolution/public/transcripts/ideology\\_transcript.html](http://hrst.mit.edu/hrs/evolution/public/transcripts/ideology_transcript.html)

Matthen and Ariew, 2002. "Two ways of Thinking about Fitness and Natural Selection," *Journal of Philosophy*. 94: 55-83.

Provine, 1988. *Sewall Wright and Evolutionary Biology*. University of Chicago Press

Woodward, 2004. *Making Things Happen: A Theory of Causal Explanation*. Oxford: Oxford University Press.

Zuckerkandl, E. and Pauling, L. 1965. "Evolutionary divergence and convergence in proteins." In *Evolving Genes and Proteins*, ed. By Bryson and Vogel. New York: Academic Press.