

**Genetic Variation**  
**The Neutralist/Selectionist Debate**

by Tristan Grimmer

It is mutation at the molecular level that ultimately leads to variation within a population and gives natural selection its sustenance. It is quite plausible to argue that everything that makes a human being a human being has resulted from mutation at a genetic level and the selective pressures of the environment. The purpose of this report is to discover the nature of genetic mutation. Does it happen by chance, or are certain mutations selected for in a population? Contention over this issue has been present since the late 1960's when Motoo Kimura developed a neutral theory of genetic mutation. In the words of Roger Lewin the debate is stated such:

To selectionists most mutations are either beneficial or harmful; beneficial ones are retained in the population, creating extensive variation, while harmful ones are removed. To neutralists, most mutations are adaptively neutral, and therefore become fixed in the population because their presence poses no harm; extensive variation is the result (1996:96).

The selectionist position seems to be logical in a Darwinian sort of way. The neutralist position, however, needs a bit more explanation. How does an adaptively neutral or equivalent change (one that isn't 'seen' by natural selection) become fixed in the population? The answer is genetic drift. Here, the idea is that the ratio of one gene over another, say a mutated version versus the original, fluctuates over generations but eventually settles to 1 or 0. A thought experiment can be used to illustrate this, or, if you have an excessive amount of free time, you can actually try it. Take 10 coins, 5 heads and 5 tails, choose 5 of them at random and remove them, this step represents the coins

that came to an untimely death. We chose randomly because of the assumption that natural selection has no effect on whether heads are better than tails. Now make the remaining 5 coins have children and boost the population back up to 10, but keep the ratio of heads to tails the same. For example, if you had 2 heads and 3 tails then after reproduction you should have 4 heads and 6 tails. Repeat this process a few times and before you know it all your coins will be heads or tails. The mutation has become fixed in the population and natural selection contributed nothing.

Our job now is to determine what is really going on and so we turn our attention to the predictive aspects of each theory. It turns out that the predicted rate at which mutations accumulate is different for each hypothesis. If the selectionists are correct then mutations cannot accumulate as fast because Natural Selection keeps on removing deleterious mutations. The rate at which mutations accumulate for the neutral theory will be much higher since they aren't constantly being removed. One example of supposed evidence in favour of the neutral theory came with the analysis of mutations at different positions on a codon. A codon is a sequence of 3 nucleotides that encodes for a specific amino acid. In general, if either of the first 2 nucleotides of a codon changes, the resultant amino acid is different. The 3rd site, however, is usually silent; a change here does not change the amino acid. A mutation at this site is called a synonymous substitution. It was found, by comparing two species of sea urchin, that there were 5 mutations at such sites in the gene that coded for the protein histone IV. These 5 mutations were located within a stretch of only 11 codons, apparent confirmation of the neutral theory. Other data, such as an analysis of RNA viruses, also seems to confirm the neutral hypothesis. RNA has an

intrinsically higher rate of mutation. The neutralists argue that since the rate of accumulation of mutations is high as well, that it is in keeping with the Neutral hypothesis. But wouldn't a higher intrinsic rate of mutation also lead to a higher number of favourable mutations that would be kept under the selectionist scheme also?

According to Roger Lewin "The question is, therefore, whether the observed maximum rate of change better fits the predicted effects of selection or the random accumulation of neutral alleles. The answer, unequivocally, has been the latter, and represents strong support for the neutral theory(1996: 101)." Always beware of words like "unequivocally". Remember the synonymous substitution example? Well, it doesn't seem too amazing that it obeys the predicted results of the neutral theory because the sites where mutations were looked at were silent, they were already known not to make any difference in the protein! It seems a little obvious that such a change would be invisible to the selective pressures of the environment. In a paper by Tomoko Ohta the situation is described more accurately.

DNA sequence data have rapidly increased in the nineties, enabling comparison of the patterns of substitution at selectively important (such as nonsynonymous) and unimportant (such as synonymous) sites.

Unimportant sites evolve as predicted by the neutral theory, whereas important sites are more influenced by natural selection, and the difference in the patterns provides an opportunity to detect selection. Many scientists have now recognized that the strictly neutral theory is not satisfactory, and the issue has entered into a new phase(1996:95).

There is more direct refutation of the neutral theory. John Gillespie, a long-time critic of the neutral theory, has looked at the variance in the number of mutations in set lengths of DNA. According to a purely random sprinkling of independent substitutional mutations, roughly a poisson distribution if the neutral theory is correct, the ratio of the variance in the number of mutations to the average number of mutations should be one (Harvey, 1991 :65). In actual studies the ratio is found as much higher than one; somewhere around 3 for mitochondrial and nuclear DNA, and even as high as 35 for amino acid substitutions. Even for silent substitutions the number is large. The point here is that the measured values show much higher variance in the number of mutations for strings of set length. Something more than selectively neutral effects are having an influence. The initial assumptions must be wrong and the mutations aren't, in fact, independent and evenly distributed. This leads us into a discussion of constructs called "fitness landscapes" or "molecular landscapes".

Molecular landscapes are used to describe the dependence of mutations to each other and help explain the results of the variance being too high. The idea was adapted by Gillespie to the field of molecular evolution. Here is a description.

At any point in time, the fixed allele at a locus is the most fit in the current environment among those alleles one mutational step away. When the environment changes, a previously deleterious allele may become favoured, and become fixed in the population. Now a set of mutants can

be produced that are two mutational steps away from the previous fixed allele. One of these new mutants may be fitter than the currently fixed allele, and become fixed in the population." (Harvey, 1991:66)

The behaviour of systems like these is complex, but, with considerable hand-waving, can be described as motion along a mountainous surface. A specific position on the surface represents a particular sequence of nucleotides. Neighbouring positions represent nearly the same sequence, but with one mutational substitution. The actual topology of the landscape is defined by the selective pressures of the environment. We will assume that the environment is unchanging and the landscape, therefore, static. What happens is that mutations move an individual along the landscape. Mutations that lead to a higher 'altitude' are fitter and selected for, while mutations that lead lower will be selected out in a few generations. Conceptually, the neutral theory would have us believe that the landscape was flat; a movement in one direction no more fit than that of another. Stuart A. Kauffman has done considerable work on fitness landscapes and describes a populations movement on it. "Over time the cluster of individuals representing the population will flow over the fitness landscape. In the simplest cases, the population will climb to and cluster about one of perhaps a large number of different peaks. In more complex cases.. ." (Kauffman, 1993:34). Basically, a hill-climbing heuristic is being employed by evolution to get as high as possible from the current position. An interesting note on these types of problems is that you rarely get to the globally highest peak with such algorithms, but rather to a local maxima. I'm sure many hikers can attest to this fact as they look across the chasm between the peak they're on and the (higher)

peak they wanted to be on (we'll assume these were relatively ill-prepared, GPS-less, Urban-type hikers). Evolution, then, even under this model, will not find the optimal sequence of nucleotides for a given environment. It should be stated that these problems are mathematically intractable, or at least nearly so. The fitness landscapes are usually not static and their shape is hard to determine. As a result, the predictive power of the selectionists theories are much weaker.

In light of all these developments the neutral theory has had to adapt. The original formulation did allow for some selective effects but it was amended, by Kimura, to allow for more. Martin Kreitman describes the situation. "Kimura's own descriptions of the neutral theory were not always consistent with respect to the inclusion of weakly selected mutants (1996: 102)." Kimura had stated "if a mutant has selection coefficient much smaller in absolute value than  $1/(2N)$ , it behaves like a neutral mutant", however, later he is quoted as saying "all that is required is that the resulting difference in fitness be small, say, for example, less than  $1/(2N)$  (1996:102)." Who knows what N is, the point is the wording change from "much smaller" to "less than". Kimura is allowing for larger selective effects in his theory. The neutral theories that allow for some degree of selection are called nearly neutral theories. But why modify the name? Isn't this just the selection theory?

"Discrimination between the selection theory and the nearly neutral theory from these observations as very difficult. Indeed, the two theories are not quite distinguishable conceptually. Considering the ubiquity of weak selection at the molecular level, both

random drift and selection influence the behaviour of most mutants at the protein level, i.e. they belong to the nearly neutral class. No clear distinction can be drawn between the nearly neutral and selection theories (Ohta,1996:96)." Although it is not within my demesne, I will venture a guess as to why the strictly neutral theory (the "strictly", of course, had to be introduced to alleviate any ambiguity when talking about the neutral theory) had support for so long. It was, perhaps, a misuse of Occams Razor. The neutral theory certainly is simpler, and consequently has more predictive power. But a simpler theory should not be chosen when a more complex one describes the experimental results more accurately. The problem is the lack of a predictive complex model. Some degree of pride may also have been involved in not admitting that things are more complex than with the strictly neutral theory. But perhaps such defensiveness is not warranted.

The neutral theory, although not acceptable as a theory of mutation at all sites, is extremely useful. It describes the process of mutation at synonymous sites and on "introns"; segments of DNA that are edited out during replication. It's predictive power can be used, in collaboration with stochastic molecular clocks, to reconstruct phylogenies. Furthermore, the strict neutral theory acts as a null hypothesis for any investigation into molecular evolution. Any theory that attempts to fit the data can be constructed on top of the neutral one. Although we were not quite able to answer our original query "What is the nature of genetic mutation?", we were able to conclude that it is more complex than simple random chance. There is enough ambiguity to allow natural selection to play some sort of role in the evolution of our species, and in my opinion, a more than insignificant one.



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