James F. Crow and the Stochastic Theory of Population Genetics

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ABSTRACT Research in population genetics theory has two main strands. The first is deterministic theory, where random changes in allelic frequencies are ignored and attention focuses on the evolutionary effects of selection and mutation. The second strand, stochastic theory, takes account of these random changes and thus is more complete than deterministic theory. This essay is one in the series of Perspectives and Reviews honoring James F. Crow on the occasion of his 95th birthday. It concerns his contributions to, and involvement with, the stochastic theory of evolutionary population genetics.

STOCHASTIC (or random) changes in allelic frequencies can arise in at least two situations in evolutionary genetics. The first of these occurs when the fitnesses of various genotypes change from time to time and place to place as a result of unpredictably fluctuating environmental conditions. The second situation occurs when there is no selection involved. Just as a fair coin is unlikely to give exactly 50 heads from 100 tosses because of the randomness involved in the coin tossing, so also can random changes in allelic frequencies be expected to arise purely by chance in any population, even without any selective pressures. Since the second form of stochastic change in allelic frequencies in a population has received far more attention in the literature than the first, and has seen two separate but related major controversies, this essay concerns only Crow's involvement with the theory concerning this second form of change and its relevance.

The first controversy concerned the overall general evolutionary ideas of the two of the early giants of population genetics theory, R. A. Fisher and Sewall Wright. (The third early giant, J. B. S. Haldane, was not involved in this controversy.) Both aimed at fusing Darwinian theory with Mendelian genetics, and both (with Haldane) succeeded in this aim. There were, however, inevitably points of difference between the emphases that they respectively placed on the importance of the various factors involved in evolution, of which two are relevant here. First, while both discussed the effects of random changes in gene frequency from one generation to the next, Wright saw more importance in these than did Fisher, whose work focused more on the changes brought about by natural selection. [This is not to say that Fisher ignored stochastic factors: an entire chapter in Fisher (1930) was devoted to the stochastic theory, and it was as a result of his analysis in that chapter that Fisher arrived at the view that, on the whole, stochastic factors are less important in evolution than are selective pressures.] Second, although Fisher did consider interactive selective effects at several loci, as shown by his work on the evolution of dominance, he focused mainly on the analysis of the evolution of the allele frequencies one locus at a time, assuming that an entire genome evolution could essentially be analyzed by "pasting together" single-locus analyses. Wright, on the other hand, focused on the evolution of beneficial interactive genetic systems involving many loci by an interaction of random genetic drift and natural selection. Their different viewpoints on these two aspects of evolution led to the controversy between Fisher and Wright.

Wright's "interactive" viewpoint can be illustrated by the following simple example. Suppose that in some population the only extant genotype at two gene loci, A and B, is the double homozygote *aabb*. Suppose further that two new alleles, *A* and *B*, arise at these loci respectively by mutation and that *A* and *B* are unfavorable individually (*e.g.*, in the genotypes *Aabb* and *aaBb*). Then, under natural selection alone, the alleles *A* and *B* will not begin to spread throughout the population. Suppose, however, that these new alleles are favorable in combination, so that, for example, the

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double homozygote *AABB* is the most fit genotype and in particular is more fit than the original genotype *aabb*. Wright felt that the eventual fixation of *AABB* would be difficult in a large population because of the initial selective disadvantage of *A* and *B* individually. He argued that fixation of *AABB* would arise best in some small, perhaps geographically isolated, subpopulation in which the population size is so small that random changes in gene frequencies are important and could overcome the initial selective disadvantage of *A* and *B*. These stochastic changes could then lead to creation of individuals of the *AABB* genotype in that subpopulation.

This process is only the first phase in Wright's three-phase process. In the second phase, the genotype *AABB* becomes essentially fixed by selection in the subpopulation in which it arose. This is often described by saying that, by random genetic drift, the population crosses a valley between the two peaks in a selective "adaptive landscape" corresponding to the favored genotypes *aabb* and *AABB*, a procedure that would not happen under Fisher's "pasting together" paradigm. In the third phase, the favored genotype *AABB* is exported to other subpopulations by migration and then fixed in the population at large by selection.

All three phases of the Wright paradigm led to controversy. In particular, the reliance on stochastic changes in the first phase of the process became blown out of all proportion in the ensuing discussions, with one extreme (and wrong-headed) view being that Wright had replaced selection by random genetic drift as the main agent for evolution. Although Crow worked closely with Wright for 30 years, I do not recall, in the many conversations that I had with Crow on this topic, his supporting Wright's paradigm. I suspect that this was because he felt that, for it to work often, the paradigm requires unrealistically finely tuned relationships between the subpopulation sizes, the population substructure, the migration rates between subpopulations, and the selective values, as well as the recombination rate between the A and B loci involved. Furthermore, one can argue that because the numerical values of these quantities are in practice normally unknown, any argument about the merits of the "shifting balance" theory can exist only in an ivory tower. In what is by far the best-informed, balanced, and thoughtful discussion of this controversy, Crow (2008) appears to me to come to essentially this view, and possibly for this reason the controversy has largely died down in the last two decades, as Crow (2008) also states. For further discussions of both sides of the theory, see Coyne *et al.* (1997, 2000), Crow *et al.* (1990), and Wade and Goodnight (1998, 2000).

Despite the claim made above that Crow did not in general support Wright's viewpoint, there is one reason why one might have suspected that he would be sympathetic to it. Just as, by chance, a fair coin toss can quite easily give three or fewer heads in 10 tosses but is extremely unlikely to give 30 or fewer heads in 100 tosses, so also stochastic changes in allelic frequencies in a small population are more important than those in a large population. Thus the size of a population is a central component in discussing the relevance of stochastic changes in allelic frequencies in that population. Of course this is not the end of the story: the number of breeding individuals at any time, rather than the total population size, is closer to what matters, but even this is insufficient. What is really important is the so-called effective population size, usually denoted N_e, and originally developed by Wright (1931), who considered two definitions of this concept. The first of these aspects, the variance effective population size, is "forward-looking" and defined in terms of the variance of the change in the frequency of some allele from one generation to the next. The variance effective population size is small if this variance is large, and when this is so there is a more important role for random changes in allelic frequency. The second aspect, the inbreeding effective population size, is "backward-looking" and defined in terms of the probability that two genes taken at random in some generation are both descended from the same gene in the previous generation. If this probability is comparatively large (as occurs, *e.g.*, when a small number of individuals contribute much more than their fair share to the genetic make-up of the next generation), then the inbreeding effective population size is small, and, when this is so, there is again a more important role for random changes in allelic frequency. For a population whose size remains constant from one generation to the next, then (at least in the simple models that Wright considered), the two definitions lead to the same value of N_e, and Wright appears to have used the two concepts interchangeably. Unfortunately, for populations the size of which changes from one generation to the next, and in particular for the human population, the two definitions lead to different values for N_e. Crow (and colleagues) were the first to point this out (Crow 1954; Crow and Morton 1955; Kimura and Crow 1963) and to investigate systematically the properties of the concept, an investigation that continues to this day (see, *e.g.*, Sjödin *et al.* 2005).

Perhaps the most important outcome of these investigations is that the effective population size (under any definition) often assumes a value far less than the actual population size. For example, in a population with 10 breeding males and 1000 breeding females in each generation, all definitions lead to a value of N_e at $\sim$40. This small number allows substantial random changes in gene frequencies from one generation to the next, even though the actual population size is quite large. In fact, even with 10 breeding males and 1,000,000 breeding females in each generation, the value of N_e is still $\sim$40. The small effective size derives from the fact that half the genes transmitted from one generation to the next come from the small number of males in each generation; the actual number of females, as long as it is large, is comparatively unimportant to the numerical value of N_e. Stochastic events are relatively important in populations having small effective population sizes. Armed with this knowledge, one might have expected that Crow

would have been more favorably disposed to the Wright's paradigm than (at least in my judgment) he was. I have indicated above why I suspect that he arrived at the position that he did.

One benefit arising from the discussion about the importance of stochastic factors in genetic evolution was the development of substantial theory concerning these factors. This eventually led to the second, and more central, controversy in the field. Armed with various results from the stochastic theory of population genetics to which he had so significantly contributed, as well as with knowledge of the extent and pattern of the genetic variation that in the 1960s was beginning to be observed in natural populations, Kimura (1968, 1971) introduced the so-called neutral theory. According to this theory, the observed genetic variation did not have a selective explanation, but instead arose from random changes in the frequencies of selectively neutral alleles. Correspondingly, the theory also claimed that many, perhaps most, of the allelic replacement processes making up the course of genetic evolution were not driven by selection, but instead came about because of these random changes.

Before discussing further aspects of the neutral theory it is necessary to discuss the background against which Kimura put the theory forward. The most important part of this background is the evolutionary model used at the time, which reflected contemporary knowledge about the nature of a gene. This was the so-called "infinitely many alleles" model. The central assumption of this model, inspired by the DNA nature of the gene and the consequent vast number of possible alleles (DNA sequences) at any gene locus, is that because any base change is likely to lead to a DNA sequence not currently observed in a population, each mutation is of an entirely new allelic type.

As an initial step in assessing the validity of the neutral theory, it was necessary to compare the extent of genetic variation observed in natural populations with what would be expected under that theory, assuming the infinitely many alleles model. The theoretical prediction for the genetic variation expected is conveniently measured by the probability that any individual taken at random is heterozygous at any neutral gene locus. Well before the neutral theory was put forward, and even before the detailed nature of DNA was known, Malécot (1948) had considered the infinitely many alleles model and had arrived at the explicit formula $\theta/(1 + \theta)$ for this probability, where $\theta = 4Nu$, N being the population size and u the rate of mutation to new allelic types at this locus. Clearly, the larger the mutation rate, the larger the probability, as expected. (The dependence on the population size is less intuitively obvious.) Kimura and Crow (1964) referenced Malécot's work, but gave a far simpler derivation of the probability $\theta/(1 + \theta)$ than had Malécot and also generalized it to the case where $\theta = 4N_e u$, N_e being the inbreeding effective population size. While the formula $\theta/(1 + \theta)$ provides only one characteristic of the nature of neutral genetic variation under the infinitely many alleles model, namely its extent, it did lead to a beginning of the analysis of the forces leading to the observed patterns of genetic variation in natural populations. In my concluding comments I refer to the question of the pattern, as opposed to the extent, of genetic variation expected under the neutral theory.

Inevitably, the neutral theory became controversial. Again one could recognize, as with the arguments concerning the shifting balance theory, a "selective" and a "stochastic" camp. Many selectionists dismissed the theory out of hand. However, there is nothing in the theory of population genetics to deny its possible validity. Since Crow had worked very closely with Kimura for more than a decade before the theory was proposed and for several decades afterward, he was closely associated with the main protagonist on one side of the argument. However, as with the shifting balance theory dispute, he maintained an objective viewpoint on the question of the importance and validity of the neutral theory. His article reviewing the arguments on both sides (Crow 1972) was insightful and fair to both sides. Many (including myself) asked him often what his views on the neutral theory were. His reply to those who asked this question were disarming to those of a controversial disposition, and his tact in discussing the theory went a long way to defusing controversy.

As with the argument on the merits of the shifting balance theory, less rigid views have developed on all sides over the years, and the final verdict on the neutral theory is still some way off. No doubt there are loci at which the alleles present are selectively neutral at some time or in some place, and no doubt there are cases of selective differences. It is probably impossible to reach any conclusive statement about the validity of the theory, given our lack of knowledge of these matters. Crow has performed an invaluable service in helping to make this fact clear, to tone down the controversies, and to bring about a more balanced discussion on the topic.

Crow's earlier research interests included the analysis of the mutation/selection equilibrium that arises when a selectively disadvantageous allele is maintained in a population by mutation from the favored allele. It is therefore interesting that he did not comment on the extension to the neutral theory, made by Ohta (1976), that most gene replacement processes in evolution occurred by stochastic processes leading to the fixation of slightly selectively disadvantageous alleles in a population. No such fixation is possible under a deterministic (*i.e.*, nonstochastic) analysis. Ohta's view was supported by the claim that, although a selectively disadvantageous mutation is less likely to be fixed in a population than a selectively neutral mutation, many more selectively disadvantageous mutations are likely to arise in a population than selectively neutral mutations. Again, Crow did not comment publicly on this (even more controversial) theory, again acting behind the scenes in toning down the controversies surrounding the theory.

In discussing the theory relating to the infinitely many alleles model and its relevance to the neutral theory, Crow (1972) asked an interesting question that has led to a major shift in the direction that population genetics theory has taken over the last three decades to a new, retrospective, position. If we are given a sample of genes at some locus, displaying a collection of various allelic types, one possible analysis of the neutral theory relies on identifying the oldest allele in this sample. Of course we do not know which of the alleles observed in the sample is the oldest, but we do know which is the most frequent. Crow's question was: "What is the probability that the most frequent allele in the sample is also the oldest?" This is not an easy question to answer, but in work that has had implications far afield from genetics (see, *e.g.*, Watterson and Guess 1977; Bingham and Goldie 2010) the mathematical formula for this probability was eventually found.

The retrospective theory, looking backward in time, focuses on asking questions about the forces, in the past, that led to the currently observed genetic phenomena. The neutral theory itself is a prime example of this. There were, perhaps, two main reasons for this change in direction of population genetics theory toward a retrospective analysis. First, the original aim of population genetics theory—to show that biological evolution is a direct consequence of Mendelian inheritance in outbreeding populations—had by that time been accomplished. Second, the nature of the data becoming available invites such a retrospective analysis. The massive amount of genetic data now becoming available has led to significant advances in population genetics theory needed to analyze these data.

It is a pleasure to conclude on a personal note. First, Jim's ability to see questions clearly, to synthesize the various aspects of any question and thus help to resolve it, were and still are unmatched. He helped me, and many others, understand issues clearly. Second, it is hard to think of anyone who comes even close to Jim in influencing and helping forward the careers of so many. Jim helped me on many occasions in my career, always constructively, for which I owe him an immeasurable debt. I wish to record here one specific example. As stated above, a more complete assessment of the validity of the neutral theory requires an analysis not only of the extent of, but also of the patterns of, the genetic variation one would expect to see in a sample of genes from a population if the neutral theory were true. I was fortunate to work with Jim on this question in early 1971, when we were both (by chance) on leave together at the University of Texas in Austin. Jim refused to be joint author of the article (Ewens 1972) that eventually provided the desired answer to the "pattern" question, claiming (characteristically and incorrectly) that his contribution did not warrant it. Thus I received sole credit for the work, and this significantly advanced my career. In owing this and many other debts to Jim, I am not alone: Hartl (2011) has made analogous comments for himself, and many others in this sequence of tributes to Jim will certainly say something similar.

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