

# Perspectives

## Anecdotal, Historical and Critical Commentaries on Genetics

### Wright and Fisher on Inbreeding and Random Drift

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#### ABSTRACT

Sewall Wright and R. A. Fisher often differed, including on the meaning of inbreeding and random gene frequency drift. Fisher regarded them as quite distinct processes, whereas Wright thought that because his inbreeding coefficient measured both they should be regarded as the same. Since the effective population numbers for inbreeding and random drift are different, this would argue for the Fisher view.

SEWALL Wright and R. A. Fisher were central figures in mathematical population genetics; along with J. B. S. Haldane they effectively invented the field and dominated it for many years. On most issues the three were in agreement. In particular, all favored a neo-Darwinian gradualist approach and believed in the importance of a mathematical theory for understanding the evolutionary process. Yet on a few questions Fisher and Wright differed profoundly and argued vehemently. Fisher was contentious and was often involved in controversy, frequently attacking his opponents mercilessly. Wright, in contrast, was very gentle to most people. But there were a few exceptions and Fisher was one. Haldane mostly stayed out of the arguments between them.

One question on which the two disagreed was the importance of random gene frequency drift and its role in Wright's shifting-balance theory of evolution. Wright thought that a structured population with many partially isolated subpopulations, within which there was random drift and among which there was an appropriate amount of migration, offered the greatest chance for evolutionary novelty and could greatly increase the speed of evolution. Fisher thought that a large panmictic population offered the best chance for advantageous genes and gene combinations to spread through the population, unimpeded by random processes. They also disagreed on dominance, Fisher believing that it evolved by selection of dominance modifiers and Wright that it was a consequence of the nature of gene action. These differences were widely argued by population geneticists in the middle third of the twentieth century, and the interested community divided into two camps. Although the issues are not settled, Wright's shifting-

balance theory has less support than it formerly had. As for dominance, there is general quantitative disagreement with Fisher's explanation of modifiers, but other mechanisms (*e.g.*, selection for more active alleles) have to some extent replaced it. Wright's theory remains popular and has been generalized and extended (KACSER and BURNS 1973).

#### DISAGREEMENTS BETWEEN WRIGHT AND FISHER

In the early years, the two men had a collegial relationship. Their approaches were quite different, but they exchanged letters and compared results. Sometimes one would correct the other's errors, and the corrections were gracefully and gratefully accepted. I should emphasize that, aside from such details, which were quickly straightened out, there was never any disagreement between Fisher and Wright about the underlying theory. Their differences were in interpretation, not in the mathematics. Although their techniques were different, for any particular problem (and they often considered the same one), their theoretical conclusions were the same. This happy situation prevailed until around 1930. Then something went wrong. I do not know exactly what happened, but one thing seems to be important. Wright's famous paper (WRIGHT 1931) was largely written several years before publication and he sent a manuscript copy to Fisher, who was then working on his book (FISHER 1930). Wright's paper had an error, later corrected, but this was not pointed out by Fisher. Furthermore, some of Wright's formulas appeared later in Fisher's book. Wright thought that Fisher deliberately did not tell him of the error and that he appropriated some of Wright's results in his book (PROVINE 1986, pp. 259–260) (this agrees with what Wright told me). It is possible that, since their

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notation and methods were so different, it was hard to translate from one to the other, and since he knew how to solve the problems, Fisher simply did not realize that Wright had already arrived at some of his results. In any case, this had a profound effect on Wright, and they no longer were on friendly terms. Correspondence ceased and Wright thereafter never sent manuscripts to colleagues prior to submission. The best source of information about this fascinating period is PROVINE (1986), which gives a very complete history. Of special interest is Provine's including virtually the entire correspondence between the two giants.

For many years, after Fisher's death in 1962, and until his own in 1988, Wright continued to write, repeatedly supporting his views and especially his shifting-balance theory. Counterarguments made by others were that his preferred population structure with subdivisions and appropriate balance of selection, mutation, random drift, and migration is very rare and that while his mechanism is at work the population fitness is substantially reduced. A process that produces a loss of fitness, even if temporary, is not very inviting. Recently the argument has died down as Wright's model has had less support. Stimulated by the great power of molecular techniques and ever-faster computers, the emphasis has become more on obtaining and examining the data rather than supporting a particular theory. Toward the end of his long life, Wright became more conciliatory (WRIGHT 1988). As to the different approaches of Haldane, Fisher, Kimura, and himself, Wright wrote "All four are valid."

#### INBREEDING AND RANDOM DRIFT

Another difference of viewpoint between Wright and Fisher has had much less attention and created much less rancor. Yet it was a significant source of disagreement. The issue was inbreeding *vs.* random gene frequency drift. Random drift is especially important in small populations where random mates may be related and share a fraction of their genes. Nonrandom consanguineous matings of course can occur in populations of any size. In many ways the two processes are similar; in particular, both lead to an increase in homozygosity and ultimate fixation. Should they be regarded as the same thing?

Fisher regarded them as quite different, as shown by the following quote:

I should mention the theory of inbreeding (FISHER 1949) and the study of such lineages as are produced by a predetermined mating system. . . . I do not think it would be helpful to consider the study of inbreeding as a part of population genetics, though undoubtedly the lineage is not an individual, but a concatenation of individuals. The genetic properties of an inbreeding system are very simply expressed in terms of matrix algebra; the breeding system defines the generation matrix, a mathematical operator transforming each generation into the next. . . . I doubt

that any modern worker on inbreeding is tempted to overlook these differences. (FISHER 1953, p. 512)

Fisher did not consider the irregular consanguineous matings that occur, especially in animal pedigrees, and for which Wright's inbreeding algorithm is especially useful. I doubt, however, that this would have changed Fisher's opinion. He clearly thought that consanguineous mating within a large population, whether systematic or not, was quite different from increased fixation due to small population size.

Wright's view was different. He is justly famous for inventing an inbreeding coefficient and for producing a simple algorithm, learned dutifully if not enthusiastically by generations of genetics students, for computing this coefficient in a pedigree of any degree of complexity (WRIGHT 1922). Wright was particularly pleased that his  $F$  statistics could be used to measure random drift as well as consanguineous mating. In his words,

It is important to note that the same coefficient,  $F$ , that measures the degree of approach toward fixation [in a finite population] is also the Galtonian correlation coefficient  $r_{es}$  [ $F$ ] for the alleles that come together at fertilization. This is zero under random mating, 1 under complete fixation and  $F$  as the weighted average in the intermediate population. [Additions in brackets are mine.] (WRIGHT 1951, p. 324)

Since he could use the same formulas for both inbreeding and random drift, Wright naturally thought of these as two sides of the same coin. Furthermore, he could also use his  $F$  statistics to consider both processes at once; *e.g.*, consanguineous mating in a small population or subpopulation (WRIGHT 1951).

In recent years it has become more usual to measure  $F$  by probability analysis (MALÉCOT 1948) rather than by correlations. Wright, however, stuck by his guns; throughout his life he preferred correlations. One reason is that correlations, in contrast to probabilities, can be negative.

#### EFFECTIVE POPULATION NUMBER

Early on, WRIGHT (1931) introduced the popular and very useful concept of Effective Population Number,  $N_e$ . This is the size of an *idealized* population with the same gene frequency drift or inbreeding as the observed population. An idealized population is panmictic with each parent having an equal *expectation* of progeny. Note that this does not mean that each parent has the same number. Rather, the number of progeny has a Poisson or binomial distribution. In this idealized case  $N_e$  is simply the number of breeding adults. This concept of effective population has been widely used;  $N_e$  is regularly employed as a surrogate for the actual number in countless formulas.

Around 1950, while trying out various formulations, I realized that there can be more than one way to define  $N_e$ . Most important for my present purpose are defi-

nitions in terms of inbreeding and in terms of random gene frequency drift (CROW 1954). I designated these as inbreeding ( $N_{eI}$ ) and variance ( $N_{eV}$ ) effective numbers. For a monoecious population with a random amount of self-fertilization, these are

$$N_{eI} = \frac{N_{t-1} m_k - 1}{m_k - 1 + V_k/m_k}$$

$$N_{eV} = \frac{4N_t - m_k}{2(1 + V_k/m_k)}.$$

In these formulas,  $N_t$  and  $N_{t-1}$  are the population numbers in the current and previous generation,  $m_k$  is the mean number of progeny per parent (or mating pair), and  $V_k$  is the variance in the number of progeny per parent. This is the simplest case, sufficient to make the distinction clear. This theory has had much further development in recent years, especially by taking account of separate sexes and permitting selection (CROW and DENNISTON 1988) (for a particularly thorough and thoughtful review, see CABALLERO 1994).

The important point is that  $N_{eI}$  and  $N_{eV}$  are not the same. They sometimes differ considerably. As an extreme example, consider a population in which each mated pair produces exactly one progeny ( $m_k = 1$ ,  $V_k = 0$ ). The inbreeding effective number is infinite (since there is no chance for two individuals to share a common ancestor) while the variance number is  $\sim 2N_t$ . Typically, in a growing population  $N_{eI} < N_{eV}$  and vice versa in a declining population.

#### WHO WAS RIGHT?

The fact that the two effective numbers are different would seem to resolve the question in favor of Fisher's view: inbreeding and random drift are not the same thing. A single formula does not describe both.

But consider a special situation. If the population size remains constant,  $m_k = 2$ , both formulas reduce to

$$N_e = \frac{4N - 2}{2 + V_k}$$

(WRIGHT 1939, p. 21).

So, if only populations of constant size are considered, Wright's view makes sense. But of course a general

theory should not be so constricted. Remarkably, the only cases that Wright ever wrote about were those in which the two effective numbers were the same, so he naturally regarded this as additional evidence for his view that inbreeding and random drift can be dealt with the same way. As far as I know, Wright never made a mistake in dealing with this problem, for he never studied cases where the two effective numbers differed. He must have had a guardian angel that steered him away from error in choosing model situations.

Later, Wright was aware of inbreeding and variance effective numbers and discussed them in some detail (WRIGHT 1969, pp. 211–220). Yet I do not think this caused him to change his view. His discussions almost always dealt with populations in which the two effective numbers are the same.

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