

# Sewall Wright: A Life in Evolution

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Population genetics, the study of how the genetic composition of populations changes over time under the influence of mutation, migration and natural or artificial selection, is one of the few areas in biology that rests upon a thorough and rigorous theoretical foundation. This foundation is itself almost entirely the result of the intellectual labours of three people – Fisher, Haldane and Wright – largely during the first half of this century. Earlier articles in *Resonance* have outlined the contributions of R.A Fisher<sup>1</sup> and J B S Haldane<sup>2</sup> to the establishment of population genetics as a major field of study. In this article, we shall take a look at the life and work of the third member of this trio of intellectual giants to whom we owe much of our basic understanding of the mechanics of the evolutionary process.

## Biographical Sketch

Sewall Wright was born in 1889 in Melrose, Massachusetts, but spent most of his childhood years in Galesburg, Illinois, where his father taught economics and mathematics at the Lombard College. Sewall Wright was by no means an outstanding student in school, but took a keen interest in languages (Latin and German), mathematics, physics and natural history. He went on to do his undergraduate studies at Lombard College and graduated in 1911. At college too, he studied relatively little biology, concentrating more on languages, mathematics, probability and chemistry. He did, however, get some exposure to current ideas in genetics and evolution, both subjects then being in their infancy. He had also, by this time, read important books by Darwin, Wallace, Kellog, Reid, Galton and Punnett that were shaping thinking in these new branches of biology.

Also in 1911, Wright had his first exposure to active research biologists when he spent the summer at Cold Spring Harbor and

<sup>1</sup> See *Resonance*, Vol. 2, No. 9, pp 27–31, 1997.

<sup>2</sup> See *Resonance*, Vol 3, No. 12, pp 32–35, 36–42, 1998.

had the opportunity of interacting with C B Davenport and J A Harris, both biometricians, and G H Shull, a geneticist working on hybridization and breeding. Wright returned to Cold Spring Harbor again the next summer, and did some research on the distribution of freshwater and marine snails, and their parasites. He also struck up a friendship with A H Sturtevant, a student of T H Morgan, who developed the technique of recombinational gene mapping. Wright and Sturtevant were later to collaborate with T Dobzhansky on a series of problems, which we shall come to a little later in this article.

Between 1911 and 1912, Wright had obtained a Master's degree from the University of Illinois. His thesis, and his first paper, was on the anatomy of the trematode *Microphallus opacus*. In 1912, Wright joined the Bussey Institution at Harvard, working towards a doctorate with W E Castle, one of the leading American animal geneticists at the time. Also at the Bussey was E M East, another outstanding geneticist who worked with plants. Between them, Castle and East directed 40 doctoral students over a span of 35 years, including many whose names are today familiar to students of genetics: S Wright, R A Emerson, E W Sinnott, L C Dunn, C C Little and P Mangelsdorf. Wright obtained his Ph.D from Harvard in 1915 for his work on the inheritance of coat colour and other coat characteristics in guinea pigs. At that time, a major problem for geneticists was to explain results from crosses where the observed phenotypic ratios in offspring did not exactly match up to predictions from Mendel's laws. In some extreme cases, one even found a whole range of phenotypes in the  $F_2$  generation that differed only slightly from each other (graded variants). The major hypotheses to explain these cases of graded variation were based on (a) multiple Mendelian loci, (b) multiple alleles at a locus, and (c) environmentally induced variation (for more detail on loci and alleles see *Box 1*). Wright was able to demonstrate the existence of multiple agouti and albino alleles affecting coat colour, and multiple loci affecting coat roughness. He also speculated extensively on how enzyme pathways and pigment precursors

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### Box 1. Genes, Loci and Alleles

Often a non-specialist is confused by varying usage of the word 'gene'. For example, in the phrase 'the gene for eye colour', gene is being used for 'locus', whereas in the phrase 'the gene for brown eyes', it is being used for 'allele'. Basically, a gene is a stretch of DNA that ultimately fulfills a particular function, such as specifying the formation of a particular enzyme. In most plants and animals, DNA is organized into chromosomes that come in pairs (for more details on genes and chromosomes, the reader is referred to the article 'What is a Gene?', *Resonance* Vol.2, No.4, pp.38-47, 1997). Thus, most individual plants and animals have two copies of most genes, the exception being males in species with X and Y chromosomes, who have only one copy of genes on the X chromosome. The location on the chromosome occupied by a gene that controls a particular trait is called a *locus* (plural, *loci*). If we imagine the chromosome to be like a tall bookshelf with slots for different topics, then a locus is like a particular slot earmarked for, say, history. If this is the third slot from the top, in all bookshelves you will find only a history book in this third slot. However, different bookshelves may have a different history book in this slot: one may have a book by Romila Thapar, another a book by Percival Spear. Similarly, in the two chromosomes of a kind found in any individual, a particular locus may be occupied by alternative forms of the gene, called *alleles*. Thus, the DNA present at the eye colour locus may vary in nucleotide sequence such that the stretch of DNA at this locus on one chromosome specifies blue eye pigment, whereas that on the other chromosome specifies brown eye pigment. Hence, we speak of either a blue eye allele or a brown eye allele occupying the eye colour locus on a particular chromosome.

might provide the physiological basis for the observed patterns of inheritance of coat colouration, more than 25 years before Beadle and Tatum's *One Gene – One Enzyme* hypothesis. Wright's experimental work also helped convince his advisor, Castle, that his own views on the alteration of genes during the course of selection was wrong, and that his data could be adequately explained by assuming multiple loci controlling the traits under study.

From 1915 to 1925, Wright worked for the United States Department of Agriculture (USDA) at Washington DC. He then moved to the University of Chicago as Associate Professor of Zoology, and stayed there until his formal retirement in 1954. After his retirement, Wright became L J Cole Professor of Genetics (emeritus) at the University of Wisconsin, and remained there until his death in 1988. Amazingly, he was scientifically active right till the end. After his formal retirement at the age of 65, Wright published 58 papers and a monumental four volume



book, *Evolution and the Genetics of Populations*. The last three volumes of the book, and 20 of the 58 papers were published after the age of 80, and his last paper was published in the journal *The American Naturalist* a few months before his death at the age of 99! From the 1930s on, Wright achieved international fame for his work. He was elected to the US National Academy of Sciences in 1934, and the same year became President of the Genetics Society of America. He went on to be the President of the American Society of Zoologists, the American Society of Naturalists, and the Society for the Study of Evolution. He received honorary doctorates from nine universities, including Harvard and Yale, and was the recipient of many awards including the US National Medal of Science, the Darwin Medal of the Royal Society, the Balzan Prize of Italy, the D G Elliott Award of the US National Academy of Sciences, and the Weldon Memorial Medal of the University of Oxford. It is difficult to think of evolutionary genetics today without the contributions of Sewall Wright, and I discuss these in more detail in the next section.

### Sewall Wright's Work

Between 1925 and 1988, Wright increasingly published more in the field of evolutionary genetics, rather than physiological genetics, and it is for his contributions to evolutionary theory that he is famous. Yet, during the Chicago years, he was actively engaged in experimental physiological genetics research on guinea pigs, and 17 of the 18 PhD scholars he advised worked on problems in physiological rather than evolutionary genetics. One of Wright's interests during his years at Chicago was to somehow link genetics to the developmental process by understanding how alleles at different loci interacted at the physiological level to produce an observable phenotype. To this end, he continued his studies on coat characteristics in guinea pigs, and also took up genetic studies on developmental abnormalities like otocephaly (reduced lower jaw and other parts of the head) and polydactyly (extra fingers and toes). He also continued to try to interpret his physiological genetics work in terms of underlying metabolic pathways and their interactions. The

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approach to understanding development and genetics that Wright was following was, however, gradually superseded by more sophisticated genetic and biochemical studies on the fungus *Neurospora*, and ultimately eclipsed altogether by the rise of molecular genetics after the 1950s.

Wright's work on evolutionary theory, on the other hand, has endured. Much of his early work on evolution was done between 1915 and 1925, published intermittently and finally summarized in a 62 page paper entitled 'Evolution in Mendelian Populations', published in the journal *Genetics* in 1931. During this period, Wright theoretically investigated the consequences of mutation, natural selection, migration and breeding structure (e.g. inbreeding versus random mating) for the genetic structure of populations (see *Box 2*). He also took up the issue of what

### Box 2. The Genetic Composition of a Population

The study of population genetics is an exercise in understanding how the genetic composition of a population changes over time. So the first question we need to deal with is: how do we characterize the genetic composition of a population? If we consider a particular locus *A*, that has two different alleles  $A_1$  and  $A_2$ , the most obvious way of describing the genetic structure of this population, with regard to the *A* locus, is through the relative proportions of the three possible genotypes. For example, if the population consists of 1000 individuals, 500 of whom are  $A_1A_1$ , 300  $A_1A_2$ , and 200  $A_2A_2$ , we can describe the population at this locus by an array of genotypic frequencies,  $P_{11} = 500/1000 = 0.5$ ,  $P_{12} = 0.3$ , and  $P_{22} = 0.2$ . Note that the frequencies sum up to 1.0. We can also represent the genetic composition of the population at this locus in terms of allele frequencies, where  $p_1$  (freq. of allele  $A_1$ ) =  $\{(2 \times 500) + (1 \times 300)\} / (2 \times 1000)$ . Basically, we have added up the number of  $A_1$  alleles present in  $A_1A_1$  and  $A_1A_2$  individuals and divided by the total number of alleles in the population (remember, each individual has two alleles at the *A* locus). Alternatively, we can write  $p_1 = P_{11} + 0.5 P_{12}$ , and  $p_2 = 1 - p_1 = P_{22} + 0.5 P_{12}$ . This characterization of the genetic composition of a population can be extended to multiple loci and multiple alleles at a locus.

A very important result in population genetics, the Hardy–Weinberg Law, tells us that in a very large, random mating population, where no selection, migration or mutation occurs, the allele frequencies remain constant over time, and the genotypic frequencies are related to allele frequencies by  $P_{11} = p_1^2$ ,  $P_{22} = p_2^2$ , and  $P_{12} = 2p_1p_2$ . This result is important in that it establishes the inertial state of a population, telling us that there is nothing in the cycle of meiosis and fertilization during sexual reproduction that would tend to alter the genetic composition of a population over generations. With this as the base, one can incorporate the effects of factors like mutation, migration, selection and inbreeding into models of the genetic structure of populations, and ask how these factors bring about genetic change in populations.



### Box 3. Random Genetic Drift

We have seen that allele frequencies do not change over time in a large random mating population with no migration, mutation or selection. Strictly speaking, this is true only for an infinitely large population. In any finite population, allele frequencies change randomly from one generation to the next, and these changes can be quite large if the population is relatively small. Imagine a random mating population of size  $N$  individuals that is undergoing no mutation, migration or selection with regard to a particular locus  $A$ , that has two alleles  $A_1$  and  $A_2$  at frequencies  $p_1$  and  $p_2$ , respectively. We further assume that generations are discrete (i.e. adults reproduce and then die) and that the population size is constant over generations. We can visualize reproduction in such a population as being a process in which all the millions of gametes formed by the adults are collected into a pool in which male and female gametes (eggs and sperm) fuse at random to form  $N$  zygotes (fertilized eggs). Since gametes contain copies of alleles found in the adults, the allele frequencies in the gamete pool will not differ from those in the adults. The problem is that out of these millions of gametes, we are, in a manner of speaking, choosing  $2N$  gametes at random to form the  $N$  zygotes that will become the next generation. So the allele frequencies in the next generation (in this sample of  $2N$  alleles) can vary from those in the parental population purely due to sampling error. If you pick out 10 balls from a bag containing a million red balls and a million white balls, on average you expect your sample of 10 to consist of 5 balls of each colour. Yet, you may actually see anything from all 10 balls being red to all 10 being white. This is exactly what happens with random genetic drift, and the smaller the population (and therefore the sample size  $2N$ ), the greater is the magnitude of sampling error you may expect. Ultimately, of course, the population will come to consist of one allele or the other, entirely by chance (for the more statistically minded reader, this is a random walk situation, and the probability of allele  $A_1$  eventually reaching a frequency of 1.0 is nothing but its initial frequency  $p_1$ ). Thus, in the long run, drift tends to eliminate genetic variability in populations.

happens to the genetic structure in relatively small populations, where random fluctuations in genetic composition can occur due to sampling (a phenomenon called random genetic drift: see *Box 3* for details). Due to these random fluctuations, it is difficult to predict exactly what the genetic composition of a small population will be at any point in the future. What one can predict is what the probability of observing a particular genetic composition will be, and this is what Wright did. He derived the probability distribution of allele frequencies in a population subject to random genetic drift (and later verified it empirically), and also in populations undergoing drift along with selection, migration and mutation. Many of these same issues were also being studied around the same time by Fisher and Haldane, on the other side of the Atlantic. Interestingly, and

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reassuringly for population genetics, Fisher, Wright and Haldane typically arrived at very similar results even though their mathematical approaches, and the simplifying assumptions they made, were often very different. Yet, there were serious differences of opinion between Fisher and Wright on the implications of their mathematical results for our understanding of how evolutionary change occurs. These differences, in turn, provided the impetus for decades of intensive experimental work on evolution, most notably by Dobzhansky and his co-workers in the US, and Ford and others in the UK.

The first debate between Fisher and Wright arose over the issue of dominance. Very often, when two alternative forms of a gene (alleles) are together in an individual, only one of them seems to be expressed at the phenotypic level (i.e. at the level of an observable trait). For example, a human carrying an allele for brown eyes and one for blue eyes will actually have brown eye colour. Thus, of the two alleles at the eye colour locus, the brown allele is termed *dominant* and the blue allele *recessive*. Typically most mutant alleles are recessive to the wild-type (most common) allele. Fisher argued that when a mutation first arose, it was not recessive to the wild type, but that natural selection acted on other, modifier, loci that affected the expression of the mutant allele, eventually rendering it fully recessive to the wild type. In other words, Fisher thought that recessiveness evolved over time, and was not, therefore, a *de novo* property of the mutant allele. Wright felt that the selection pressures operating on these postulated modifier loci would be too small to cause any major evolutionary change. Instead, he argued that a mutation at a locus would typically disrupt the function that was performed, either by resulting in the formation of an enzyme with reduced activity, or by more complex means. In that case, an individual with one wild-type and one mutant allele, would still possess sufficient quantities of the wild-type enzyme, leading to the formation of the wild-type phenotype. Thus, in Wright's view, the recessivity of a mutant allele was a *de novo* property that arose from the physiology underlying the mechanisms of gene



action. Although Wright's view has considerable empirical support now, this debate is still ongoing: the last five years alone have seen six major review articles on this topic in leading genetics and evolution journals.

The dominance debate highlights the fact that Wright's background and research in physiological genetics left a mark on how he thought about evolutionary problems. Wright knew from first hand experience with guinea pigs how even simple phenotypic traits are often governed by complex patterns of interactions between alleles at different loci (*epistasis*, in genetic terminology). Wright was also very conscious of the fact that many loci affected multiple traits (*pleiotropy*, in genetic terminology). Thus, Wright's view of evolutionary change was one in which the organism was viewed holistically, and natural selection was seen to act upon certain combinations of genes, a multi-locus as opposed to single locus genotype view (not surprisingly, Wright was very critical of Dawkin's 'genes-eye view' of evolution when *The Selfish Gene* was published). Fisher, on the other hand, though undoubtedly as familiar with pleiotropy and epistasis as Wright was, tended to think more in terms of single locus effects being important in any given environment. More importantly, Fisher also thought that population sizes in nature were typically large enough to ignore random genetic drift, and that one particular genotypic combination would be the most fit (in the Darwinian sense of better able to produce offspring) in any given environment. Wright thought that population sizes were often not that large and that drift, consequently, had some role to play in evolution, if only as an adjunct to natural selection. More importantly, he felt that there would be potentially many genotypic combinations that would be more or less equally fit in an environment. These differences in the way Fisher and Wright viewed evolutionary change led to a long and bitter debate that assumed the proportions of a major transatlantic battle in biology. Central to this debate was Wright's Shifting Balance Theory of Evolution<sup>3</sup>, which he first laid out in two papers in 1931 and 1932.

Wright derived the probability distribution of allele frequencies in a population subject to random genetic drift, and also in populations undergoing drift along with selection, migration and mutation.

<sup>3</sup>see accompanying article for details of this theory.



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In these papers, Wright argued that the optimal conditions leading to the greatest rate of evolutionary advance were those where a large population was subdivided into a number of local sub-populations or demes, such that most, but not all, matings occurred in a localized manner among members of the same deme. In this view, neither very large random mating populations nor very small isolated ones had much scope for continuing evolutionary advance. What Wright was suggesting was that evolutionary change was a multi-step process involving a balance between the forces of natural selection (both among individuals within populations, and between local populations), random genetic drift and gene flow (migration), and that the relative contribution of these factors to evolutionary change would vary over time and space; hence the 'shifting' balance.

Wright himself did not see a serious conflict between his shifting balance theory, and the Fisherian view of evolution, largely through natural selection alone, in large populations. Yet, many people came to associate Wright's theory with the view that random genetic drift was a significant alternative to natural selection as a mechanism of evolutionary change. This led to a bitter and acrimonious debate in the literature between Wright and Fisher, Ford and co-workers in the UK: this debate continued even after Fisher's death in 1962. More importantly, the debate sparked some of the best field studies in evolution, as supporters of both Wright and Fisher sought empirical evidence favouring their points of view.

In the early 1930s, Sturtevant and Dobzhansky were planning a series of field-cum-laboratory studies on the fruit fly *Drosophila pseudoobscura* aimed at estimating what the effective size of natural populations really was, as a means of empirically determining the degree to which random genetic drift would affect their genetic composition. Much of the theory of random genetic drift had been developed by Wright and moreover, he had an obvious interest in finding out how likely it was that random genetic drift played a significant role in moulding genetic variation in natural populations. Sturtevant, although



much more sophisticated in quantitative reasoning and techniques than Dobzhansky, also felt that it would be necessary for the two of them to get some expert statistical help in both experimental design and data analysis. Consequently, he approached Wright with a suggestion that the three of them collaborate on these studies that would attempt to empirically validate many of Wright's theoretical predictions about how evolutionary change occurred. Wright agreed, and the collaboration between Dobzhansky and Wright (Sturtevant dropped out in 1936) resulted in a series of 43 papers under the title 'Genetics of Natural Populations', even though Wright was not formally listed as co-author on most of them.

Dobzhansky, himself one of the central figures in evolutionary biology from the 1930s to 1970s, exerted a tremendous influence on biologists. He was himself greatly enamoured of Wright's work and has written that he '*fell in love*' with Wright's shifting balance theory after the 1932 Congress of Genetics. Generations of evolutionary biologists throughout the world, this author included, had their first taste of evolutionary genetics from Dobzhansky's '*Genetics and the Origin of Species*'. In this book, Wright's fitness landscape makes its first appearance on page 8 of the introductory chapter. Indeed, many evolutionary biologists actually got familiarized with Wright's work through the writings of Dobzhansky, rather than Wright's own papers which are not very easy to read. Dobzhansky himself leaned very heavily on Wright for assistance in planning experiments and analyzing data.

Eventually, the papers resulting from the Dobzhansky–Wright collaboration provided important information about selection intensities, mutation and migration rates, inbreeding levels, breeding structure and effective population sizes in real populations, thereby providing much empirical embellishment for the theoretical scaffolding that Wright, Fisher and Haldane had erected. Evidence for selection acting on chromosome inversions was also found. Studies on flower colour variants in wild populations of the small desert plant *Linanthus parryae* also

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yielded important insight into the role of breeding structure and distance in causing the sub-division of populations into localized breeding units or demes. The importance of the *Linanthus* data were that it seemed that large populations of this plant, occupying a fairly uniform and contiguous grassland environment, were nevertheless subdivided into localized breeding groups that were genetically differentiated from each other largely through random genetic drift. The fact that even large populations in a fairly uniform environment (the ideal situation for the Fisherian process of mass selection to operate) showed the kind of sub-division that Wright thought to play a major role in evolution was regarded as strong support for his views.

Incidentally, it was to deal with the analysis of the *Linanthus* data that Wright developed his famous  $F$ -statistics that permit us to partition genetic divergence among populations into components due to non-random mating within populations, and the fact that the populations are reproductively isolated from each other. Unfortunately, doing justice to the  $F$ -statistics would require a full article, so I will restrict myself to saying that all measures of genetic distance between populations (these measures are the basis for constructing phylogenies, or 'family trees', using molecular genetics data) ultimately derive from the statistic  $F_{ST}$ , which measures the extent to which genetic differences among populations are due to their reproductive isolation.

On the other side of the Atlantic, the Wright–Fisher debate similarly sparked extensive field work, especially on the evolutionary maintenance of different variants of a species. In the 1940s, Fisher and Ford studied populations of the moth *Panaxia dominula* that showed fluctuations in the abundance of certain colour variants from generation to generation. Using the 'mark and recapture' technique now familiar to most ecologists, they censused the populations regularly and tried to show that the observed fluctuations in the frequencies of colour variants could not possibly be due to drift alone. This work was continued by Ford and his coworkers till the 1960s and eventually yielded estimates of selection intensities against some of the colour



variants. Once again, even though the debate was not resolved by this work, it added greatly to our understanding of the evolutionary dynamics of real populations. Similarly, decades of work on the evolutionary forces responsible for maintaining genetic variation for banding patterns within and among populations of snails was sparked off and sustained by the ongoing Fisher–Wright debate. This work, which has been the subject of books and entire special issues of journals, yielded important empirical insights into the various types of random effects that could affect populations, and how these could interact with different types of selection pressures and breeding systems.

Wright's work has stood the test of time well. Today, there is tremendous interest in the ecology and evolution of subdivided populations (now more commonly called metapopulations), something that Wright first stressed almost 70 years ago. The extensions of Wright's basic work on the genetics of small populations by the Japanese geneticist Motoo Kimura have laid the foundations for the field of molecular evolution, which is today a very active area of work in evolution and systematics. The shifting balance theory continues to inspire field workers and theorists alike and has recently been extended to the evolution of inter-species interactions. And finally, it is still impossible to teach a course in either evolution or population genetics without spending several lectures on Wright's work, which is, in a way, one of the best compliments a scientist could wish for.

It is impossible today to teach a course in either evolution or population genetics without spending several lectures on Wright's work.

## Suggested Reading

- [1] W B Provine, *Sewall Wright and Evolutionary Biology*, University of Chicago Press, Chicago and London, 1986.
- [2] W B Provine, *The Origins of Theoretical Population Genetics*, University of Chicago Press, Chicago and London, 1971.
- [3] R C Lewontin, J A Moore, W B Provine and B Wallace, *Dobzhansky's Genetics of Natural Populations*, Columbia University Press, New York, 1981.
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