

Hardy–Weinberg Equilibrium and the Foundations of Evolutionary Genetics

1. The Dance of the Genes

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The year 2008 marks the 150th anniversary of the debut of the concept of natural selection as a mechanism of adaptive evolution through the reading of papers by Darwin and Wallace to the Linnaean Society. It also marks the 100th anniversary of the enunciation of the principle defining the inertial state of populations from a genetic viewpoint through the independent publication of papers on the topic by G H Hardy and W Weinberg. In this four-part series, we will examine the significance of the Hardy–Weinberg Equilibrium as a basic model of population genetics that, in turn, forms the foundation for evolutionary genetics. In Part I of this series, we first discuss the historical backdrop to the work of Hardy and Weinberg, and introduce the basic notion of genetic equilibrium.

Evolutionary genetics attempts to understand the interaction of ecological forces and genetic mechanisms that produces biological evolution. Evolutionary change, which is often also adaptive change, occurs in response to particular challenges posed to organisms by the totality of their environment, biotic and abiotic. Some challenges can be met by an individual organism by means of making alterations to its behaviour or physiology. We sweat when it is hot, to reduce our body temperature through evaporation, and shiver when it is cold to generate heat by muscular contraction. This type of change that occurs within an individual's lifetime and helps it to better withstand the vagaries of the environment is often referred to as physiological adaptation. To an evolutionary biologist, adaptation is a populational rather than individual phenomenon, and involves changes in the genetic composition of a population over generations such that the indi-



viduals in the population are eventually better able, on average, to survive and reproduce in a particular environment.

The process of evolutionary change can be visualized, by analogy to a simple example from physics, in terms of a force acting on a body and causing the body to move along a particular path or trajectory in space. The trajectory taken by a body upon which a force acts is the result of the interaction between the net force, which itself may be the resolution of a number of forces, and the structure of the body. The same net force can give rise to different trajectories when it acts on different bodies. Conversely, different bodies acted upon by different forces may end up with very similar trajectories.

In the case of evolutionary change, the body is a population whose structure is determined by what we call the genetic architecture of fitness. Basically, different components of fitness, such as time to sexual maturity, juvenile survivorship, number of offspring and adult lifespan, are often interconnected such that evolved increases in one component of fitness lead to correlated changes in others. This network of genetic correlations between different traits relevant to Darwinian fitness is what is meant by the genetic architecture of fitness. It arises because ultimately all traits are rooted in a common underlying physiology and, in a sense, compete for a finite pool of resources that the organism possesses. The genetic architecture of fitness in a population, as well as such issues as whether the population is increasing in numbers or not, can greatly affect just how the population evolves in the face of a given selection pressure. To continue our analogy, the force acting on the population is natural selection, which is itself the result of the ecology of that population (*Figure 1*).

Natural selection itself is an extremely simple concept. There exist heritable differences among the offspring that individuals produce. If some individuals, by virtue of certain traits they possess, are better able to survive and reproduce in a particular environment than others, and if these traits are at least partly heritable, then those individuals will become more common in

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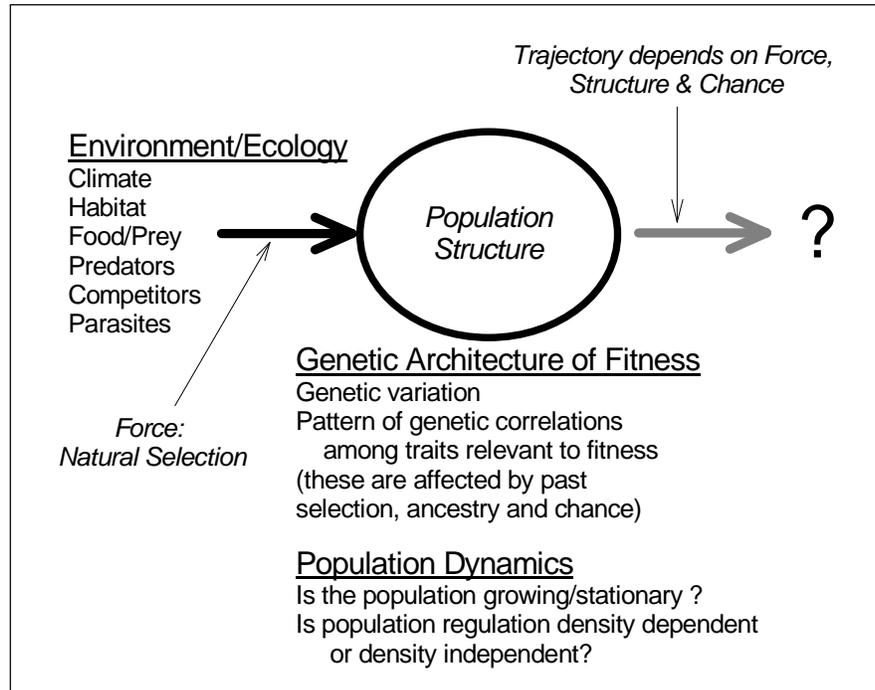


Figure 1. *The evolutionary trajectory taken by a population in a given environment depends upon the force (natural selection), the genetic architecture of fitness in that population, its population dynamics and chance.*

the population over many generations. After several generations, the population as a whole will become better adapted to its environment over evolutionary time. Thus, the complex ecology of a population, encompassing its physical environment, availability of food and the presence or absence of competing species, predators and parasites, essentially resolves into a net force of natural selection.

The Domain of Population Genetics

If the essence of evolution is change in the genetic make up of populations, then it is clear that in order to comprehend evolution we must have some means of describing the genetic composition of a population and how it changes. Or, to put it another way, we must understand how inheritance works at the level of populations rather than merely at the level of individual families consisting of two parents (or one in hermaphrodites that can self-fertilize) and their offspring. We understand how traits of the parents are inherited by offspring thanks to the work of Mendel.



The extension of Mendel's laws of inheritance to the level of entire populations is the domain of population genetics, a subject that provides evolutionary biologists a key to the language in which the greatest poem of life – Evolution – is written.

The poem of evolution cannot be read and enjoyed without knowing the language of population genetics. Descriptions of the evolutionary process couched in tongues other than population genetics are ultimately dry, and often misleading. Like translations of Ghalib or Iqbal into English, or black and white xerox copies of a vibrant colour picture, such descriptions provide but a glimpse of the beauty inherent in the process that has given rise to us as well as the living world we inhabit. The mathematical models by which a population geneticist represents the eternal dance of genes as they come together in zygotes, recombine and separate during gamete formation, and come together again as one more new generation is conceived, are as much poetry as any ghazal of Ghalib or any nazm by Iqbal. Poetry, after all, is a metaphorical representation of real phenomena and experiences; so is an algebraic statement that describes how gene frequencies change. The beauty in a poem is perceived only when one goes behind the veil of metaphor and gazes at the reality hidden beyond the words. So, too, the beauty of a model in population genetics resides not in the algebra but in what those symbols represent, which is nothing less than evolution, the very dynamics of life.

Although evolutionary genetics is somewhat more than just population genetics, it is necessary to first gain some appreciation for how genes are transmitted from one generation to the next in populations before getting into the details of how genetics and ecology interact to produce evolutionary change. In a way, population genetics tells us how the genetic make-up of populations is likely to change in certain stylised and simplified situations, assuming “all else” to be equal. Evolutionary genetics, on the other hand, explores how exactly “all else” is not equal in particular scenarios and then tries to assess the impact of this on how the genetic composition of populations changes over time.

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Mendel's Great Achievement

Imagine going to a dance performance, watching the first few minutes of an intricate group dance and then, unfortunately, getting called away to an urgent meeting. When you return, you are just in time to catch the final few minutes of the dance. Now imagine trying to reconstruct the choreography of the entire dance based on the two bits, one at the beginning and one at the end, that you actually saw! It seems incredible that such a feat could even be contemplated, let alone carried out. Yet, in essence, this is exactly what Mendel achieved almost a century and a half ago.

When Mendel began his experiments, he was continuing a long tradition of breeding and hybridisation studies that had been sparked off by the discovery of fertilization in plants by Camerarius in 1694. The next hundred and fifty years had seen numerous attempts to understand the mechanisms and patterns of heredity by crossing plants with different traits and studying the expression of those traits in their progeny. Yet, not much had been learned about the mechanisms of heredity from these studies. People had observed that if one crossed two pure breeding lines, the progeny were often uniform in appearance, resembling any one of the parental lines, but that both parental types reappeared in subsequent generations (*Figure 2*). Given the prevalent view at the time of inheritance somehow involving a 'blending' of maternal and paternal contributions, the segregation of parental types in hybrid populations was something of a mystery due to the expectation that offspring should be intermediate in appearance, as compared to their parents. Of the physical basis of heredity, nothing was known. Chromosomes were yet to be discovered; meiosis, consequently, was unknown. And it was in this milieu that Mendel proposed a theory of inheritance in 1866, based on a careful quantification of the proportions in which the different parental types appeared in hybrid generations. Mendel stated, based on his observations, that the units of inheritance were discrete and particulate, existed in pairs in individuals, and did not lose their distinct identity while in the body of offspring, such

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that when the offspring reproduced, these factors were transmitted to the next generation intact. He also did further crosses to test predictions he derived from his theory, and these largely corroborated his view.

Using modern genetic terminology, which came much after Mendel, let us now examine his explanation for observed patterns of inheritance, taking as an example the results shown in *Figure 2*. First we must distinguish between the observable characteristics of any trait in an individual (its *phenotype*), and the underlying genes that are responsible for generating that particular trait (its *genotype*). Both phenotype and genotype are

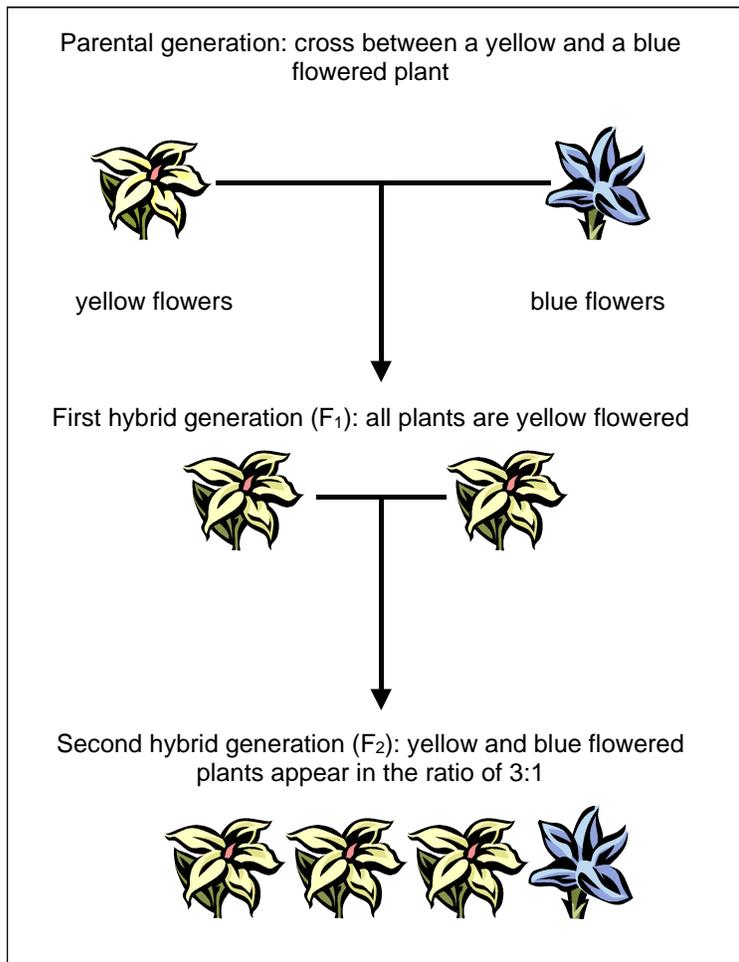
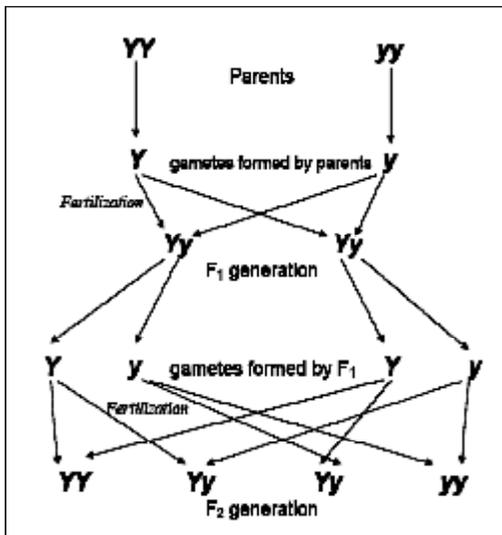


Figure 2. An example of the kind of results that Mendel observed when he crossed two pure breeding lines that differed from one another in a single trait such as flower colour, or seed colour. In the parental generation, two individuals expressing different phenotypes (manifestations of a trait: in this example flower colour) are crossed with each other. To obtain the F₂ (second filial generation), the individuals of the F₁ (first filial generation) are crossed with one another.

Figure 3. The Mendelian explanation for the kinds of offspring ratios seen in the F_2 generation in crosses such as those shown in Figure 3. Y represents the allele responsible for determining yellow flower colour, whereas y denotes the blue flower colour allele. The four possible genotypes, resulting from random fertilization among the Y and y bearing gametes produced by the F_1 individuals, gives rise to a ratio of 3 yellow (YY or Yy) : 1 blue flowered (yy) individual in the F_2 generation.



implicitly used with reference to a particular trait or traits. Mendel's theory was that each individual possessed a pair of hereditary factors (*merkmal* in Mendel's German writings) for each trait, one inherited from each parent. Thus, for example, an individual would have two factors for flower colour, one inherited from its mother and one from its father. Moreover, each of these factors would specify a particular alternative form of the trait: one factor could specify blue flower colour, another yellow flower colour. In today's terminology, we would refer to the factor for flower colour as the flower colour *locus*, and the particular form of the factor that gave rise to, say, blue flowers as the blue flower *allele* (very often, the term *gene* is used interchangeably to mean either locus or allele; this is potentially confusing and I shall, therefore, stick to locus and allele).

Mendel's explanation for results such as those illustrated in Figure 2 was that individuals from true breeding lines carried identical alleles at that particular locus (a true breeding line implies that if you mate two individuals from that line, all their progeny share the parental phenotype). Thus, an individual from the yellow flowered line would carry two alleles for yellow coloured flowers, and an individual from the blue flowered line would carry two alleles for blue flower colour (Figure 3). What

Mendel now postulated was that at the time of gametogenesis (formation of eggs and sperm/pollen), only one allele from each pair in the parent would be incorporated into each individual gamete. Thus, all gametes produced by a YY individual would carry one copy of the Y allele determining yellow flower colour, and all gametes produced by a yy individual would carry a copy of the y or blue flower colour allele. Consequently, fertilization among gametes from true breeding yellow and blue flowered parents would yield offspring whose genotype was Yy; they would carry one each of the Y and y alleles. Now, Mendel argued, contrary to the expectation

from the blending theory of inheritance, that one of the two alleles (in this example the *Y* or yellow allele) would mask the expression of the other. Thus, individuals whose genotype was *Yy* would actually be yellow flowered, and the *Y* allele would be said to be *dominant* over the *recessive* *y* allele. By invoking the concept of dominance and recessivity of alleles, Mendel provided an explanation for why all the F_1 progeny in such crosses resembled one of the parents instead of being intermediate in appearance.

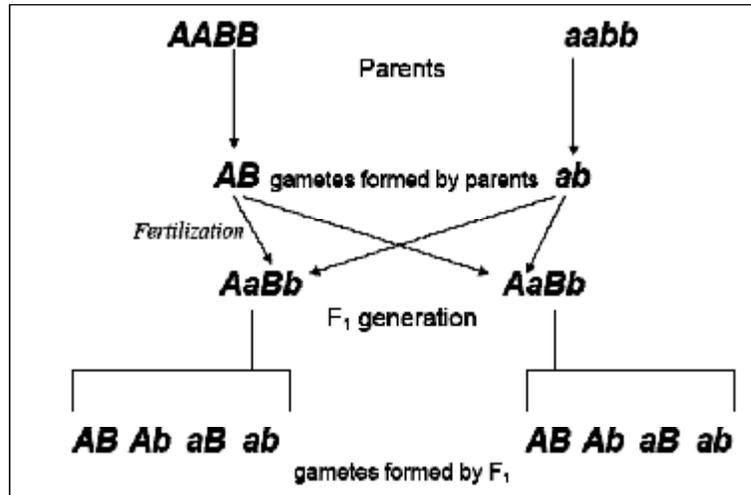
Now Mendel did something even more remarkable in the context of nineteenth century biology: he proceeded to apply probabilistic thinking (he had studied both physics and botany at Vienna during 1851–1853). When gametes were formed by the *Yy* individuals, he hypothesized, neither allele would tend to be preferentially incorporated into the gametes. Therefore, given that a very large number of gametes are typically produced by an individual, half the gametes produced by an F_1 individual could, on average, be expected to carry the *Y* allele, and half the *y* allele. Mendel further argued that the fusion of these gametes would be at random, implying that there was no tendency for a *Y*-bearing gamete, say, to preferentially fuse with another *Y*-bearing gamete during fertilization. The consequence of all this was that one could expect $\frac{1}{4}$ of the F_2 progeny to get a *Y* allele from the father and another *Y* allele from the mother, $\frac{1}{4}$ to get a *Y* allele from the father and a *y* allele from the mother, $\frac{1}{4}$ a *y* allele from the father and a *Y* allele from the mother, and $\frac{1}{4}$ a *y* allele from both parents. Thus, the genotypic ratio among the F_2 progeny would be 1 *YY* : 2 *Yy* : 1 *yy*, which, given the phenomenon of dominance, would translate into a phenotypic ratio of 3 yellow flowered : 1 blue flowered individual. This idea that particulate factors of inheritance occur in pairs and then segregate such that each gamete gets only one of the pair is often referred to as Mendel's First Law, or the Law of Segregation.

Mendel then extended this reasoning to analysing the F_2 progeny from crosses where the two parental true-breeding lines differed in two traits. To the Law of Segregation, he added the Law of

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Figure 4. A cross between two pure breeding lines differing in two traits, say flower colour and seed colour. Assume $AABB$ has red flowers and green seeds, and $aabb$ has white flowers and yellow seeds. Then all the F_1 will have red flowers and green seeds, because the alleles for red flower colour (A), and for green seed colour (B) are dominant. The F_1 progeny will produce four kinds of gamete, because, during gametogenesis, an A has equal probability of being sequestered into a gamete with B , or with b , and so on. Thus, half the A alleles will be in AB -bearing gametes and half in Ab -bearing gametes. Similarly, half the B alleles will be in AB -bearing gametes and half in aB bearing gametes. Thus, the four kinds of gamete will each constitute $\frac{1}{4}$ of the total number of gametes produced by an $AaBb$ individual.



Independent Assortment, which stated that during gametogenesis, the alleles at the two loci determining the traits under consideration would segregate independently of one another. Thus an individual with genotype Aa at one locus and Bb at the other (henceforth referred to as genotype $AaBb$) would produce four types of gamete in equal proportions: AB , Ab , aB and ab (Figure 4). The random fusion of these gametes would, thus, result in an F_2 genotypic ratio of $1 AABB : 2 AABb : 1 Aabb : 2 AaBB : 4 AaBb : 2 Aabb : 1 aaBB : 2 aaBb : 1 aabb$, which, due to A and B being dominant over a and b , respectively, would yield a phenotypic ratio of $9 AB : 3 Ab : 3 aB : 1 ab$ (AB , to be distinguished from the gametic genotype AB , represents a phenotype expressing the A and B forms of the trait) (Table 1).

One great advantage of having such a precise set of hypotheses about how heredity worked was that Mendel could empirically test the validity of his ideas by predicting in advance the kinds of progeny ratios expected in the F_1 and F_2 of certain crosses, and then comparing his predictions with the results of the crosses to assess how well his theory stood up to experimental testing. Of course, as we all know today, Mendel's Laws have, by and large, stood up to empirical testing admirably well. By 1868, Mendel had become the abbot of the monastery in Brunn (now Brno in the



♂ gametes →	1/4 <i>AB</i>	1/4 <i>Ab</i>	1/4 <i>aB</i>	1/4 <i>ab</i>
♀ gametes ↓				
1/4 <i>AB</i>	1/16 <i>AABB</i> AB (red, green)	1/16 <i>AABb</i> AB (red, green)	1/16 <i>AaBB</i> AB (red, green)	1/16 <i>AaBb</i> AB (red, green)
1/4 <i>Ab</i>	1/16 <i>AABb</i> AB (red, green)	1/16 <i>Aabb</i> Ab (red, yellow)	1/16 <i>AaBb</i> AB (red, green)	1/16 <i>Aabb</i> Ab (red, yellow)
1/4 <i>aB</i>	1/16 <i>AaBB</i> AB (red, green)	1/16 <i>AaBb</i> AB (red, green)	1/16 <i>aaBB</i> aB (white, green)	1/16 <i>aaBb</i> aB (white, green)
1/4 <i>ab</i>	1/16 <i>AaBb</i> AB (red, green)	1/16 <i>Aabb</i> Ab (red, yellow)	1/16 <i>aaBb</i> aB (white, green)	1/16 <i>aabb</i> ab (white, yellow)

Table 1. The genotypic and phenotypic ratios obtained by crossing two *AaBb* individuals, as from the F_1 , depicted in Figure 4. In each cell of the table, the proportion (of the total F_2 progeny) of each kind of progeny originating from the fusion of a particular combination of gametes is given on the top left, followed by the genotype in the middle, and the phenotype at the bottom. The proportions of each type of gamete, among all gametes produced by an individual, are similarly depicted. The genotypic and phenotypic ratios in the F_2 can be easily obtained by summing up proportions for different types of individuals represented in the table.

Czech Republic), where he had worked as a monk and, with increasing administrative duties, his research essentially ceased and he died in 1884 without having seen his work being widely accepted as was to happen a few decades later.

After Mendel

In 1875, Strasburger described chromosomes in cell nuclei for the first time and Hertwig demonstrated that fertilization involved the fusion of egg and sperm nuclei. Over the next couple of decades, a series of studies established the preeminence of the



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nucleus, and also the basic facts of mitotic (regular cell division accompanying growth of the organism) and meiotic (during gametogenesis) cell division. It was seen that chromosomes occurred in pairs and that during mitosis, each daughter cell got the full complement of two copies of each chromosome. In meiosis, on the other hand, the two members of each chromosome pair separated from each other and the resulting daughter cells that became gametes carried only one member of each chromosome pair, thus having a total complement of chromosomes that was half that present in the parent cells. This behaviour of chromosomes during gametogenesis, of course, mirrored exactly the predicted behaviour of Mendel's "particulate factors of inheritance", a fact that was pointed out independently by Walter Sutton and Theodor Boveri in 1902–1903, and has become enshrined in genetics as the Chromosome Theory of Inheritance. The realization that genes were physically located on chromosomes, in turn, led to a slight modification of Mendel's Law of Independent Assortment in the second decade of the twentieth century. I shall briefly describe this modification before going back to the story of the development of genetics in the early twentieth century.

Mendel, in a way, had been very lucky when he analysed data from crosses involving true breeding lines that differed in two traits: in all cases, the two loci in question happened to be on different chromosomes and, therefore, assorted independently just as chromosomes do during meiosis. However, if two loci are close together on a chromosome, alleles at those loci will tend to be inherited together as a unit rather than assorting independently. Thus, for example, if loci *A* and *B* as depicted in *Figure 4* were actually close to one another on the same chromosome, the *AaBb* individuals would produce only two kinds of gamete in equal proportions: *AB* and *ab*, representing the original combinations of alleles present at these loci in the two parents (*Figure 5*, consider only loci *A* and *B*). If, however, the loci are relatively far apart on the chromosome (*Figure 5*, consider loci *A* and *C*, or *B* and *C*), then there is a possibility of a cross over occurring



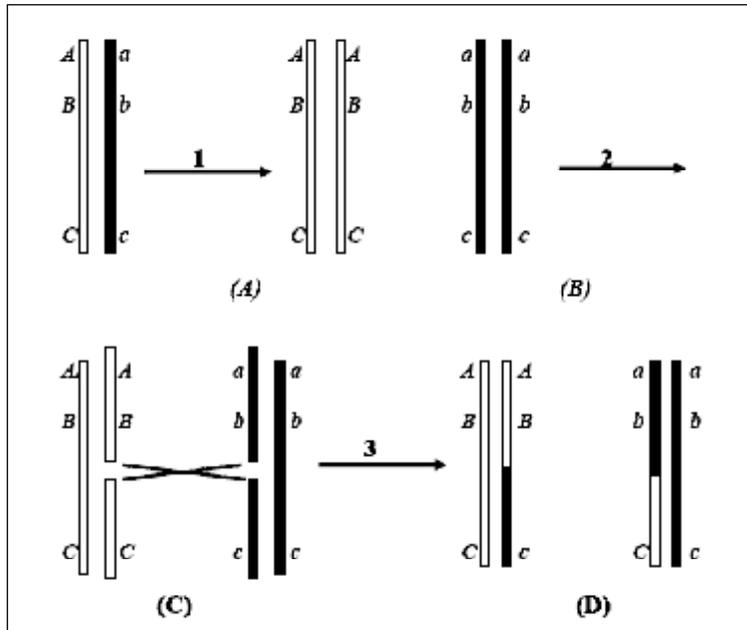


Figure 5. A schematic depiction of the genetic consequence of crossing over between homologous chromosomes during meiosis.

(A) Pairing of homologous chromosomes during meiotic prophase. (1) Replication of the chromosomes such that each chromosome is now represented by two identical chromatids.

(B) Paired chromosomes in the 4-strand stage.

(2) Breakage of one of the chromatids of each pair.

(C) Exchange of segments between the two chromatids that underwent breakage – crossing over.

(3) Sealing up of the break points in the chromatids after the exchange of segments.

(D) The four chromatids after the cross over has occurred. Each of these chromatids will form one gamete. Thus, of the four gametes resulting from this meiotic division, two will be parental types (ABC and abc), and two will be recombinants (abC and Abc) that have new combinations of alleles at the loci on either side of the cross over point.

between them during meiosis prior to gamete formation. During crossing over, segments of the chromosome are exchanged between homologous chromatids, and thus new combinations of alleles at those loci can be generated that are different from the parental combination. If a cross over occurs between two loci during meiosis, then half the gametes produced from that meiotic division carry alleles in the parental combinations, and half are *recombinants* that carry new combinations of alleles. The likelihood that a cross over occurs between any two loci during meiosis is directly proportional to the distance between the loci. The maximum frequency of recombination between loci is, obviously, 0.5, because only half the gametes resulting from a meiotic division in which crossing over occurs are recombinant. The consequence of loci being *linked* (close together on the chromosome, such that the frequency of recombination between them is < 0.5), thus, is to alter the phenotypic frequency in the F_2 such that there is a preponderance of parental types over what would be expected due to independent assortment (*Table 2*).

To return to the development of genetics, Mendel's Laws were independently rediscovered and verified in 1900 by Correns, von

♂ gametes →	$(1-r)/2$ AB	$r/2$ Ab	$r/2$ aB	$(1-r)/2$ ab
♀ gametes ↓				
$(1-r)/2$ AB	$(1-r)^2/4$ AABB AB (red, green)	$r(1-r)/4$ AABb AB (red, green)	$r(1-r)/4$ AaBB AB (red, green)	$(1-r)^2/4$ AaBb AB (red, green)
$r/2$ Ab	$r(1-r)/4$ AABb AB (red, green)	$r^2/4$ Aabb Ab (red, yellow)	$r^2/4$ AaBb AB (red, green)	$r(1-r)/4$ Aabb Ab (red, yellow)
$r/2$ aB	$r(1-r)/4$ AaBB AB (red, green)	$r^2/4$ AaBb AB (red, green)	$r^2/4$ aaBB aB (white, green)	$r(1-r)/4$ aaBb aB (white, green)
$(1-r)/2$ ab	$(1-r)^2/4$ AaBb AB (red, green)	$r(1-r)/4$ Aabb Ab (red, yellow)	$r(1-r)/4$ aaBb aB (white, green)	$(1-r)^2/4$ aabb ab (white, yellow)

Table 2. The genotypic and phenotypic ratios obtained by crossing two *AaBb* individuals, as from the F_1 depicted in Figure 4, when the loci *A* and *B* are linked with a recombination frequency of r ($0 \leq r \leq 0.5$). In each cell of the table, the proportion (of the total F_2 progeny) of each kind of progeny originating from the fusion of a particular combination of gametes is given on the top left, followed by the genotype in the middle, and the phenotype at the bottom. The proportions of each type of gamete, among all gametes produced by an individual, are similarly depicted. The genotypic and phenotypic ratios in the F_2 can be easily obtained by summing up proportions for different types of individuals over the table. It can easily be seen that setting $r = 0.5$ recovers the 9:3:3:1 ratio characteristic of independent assortment, but that values of $r < 0.5$ give rise to ratios deviant from 9:3:3:1, especially in terms of more individuals of the *ab* phenotype than expected under independent assortment.

Tschermak and de Vries. The young science of genetics thus acquired a firm foundation upon which an imposing edifice was rapidly erected. In another five decades or so, the locations of genes on chromosomes were being mapped in many organisms, the functioning of genes through coding for enzymes was understood and DNA had been identified as the genetic material and its double helical structure had been elucidated. Today, of course, Mendel’s particulate factors of inheritance, much like atoms



which started off as abstract entities and then acquired a structure, can be manipulated, split, recombined and harnessed for practical purposes. Alongside the understanding of how genes produced phenotypes, a conceptual unification of great importance to biology also took place during the early decades of the twentieth century. Out of this unification flowed a detailed understanding of the genetics of the evolutionary process, often termed the Synthetic Theory of Evolution, or the Neo-Darwinian Synthesis. However, in order to examine this development in some detail, we need to go back in time once more to the era of Mendel, and take a look at the work of the other towering figure in biology, Charles Darwin.

Darwin, Mendel, and the Synthetic Theory of Evolution

Even before Darwin and the publication of *On the Origin of Species* in 1859, many thinkers had begun to argue for a process of evolution – descent with modification – as opposed to supernatural creation of all species as they were, as an explanation for the observed patterns of diversity of life forms. In many ways, the fundamental issue before biologists in the eighteenth and nineteenth centuries was to explain the adaptiveness of species, the relatedness of species, and the diversity of species. The religiously inspired view that species were individually created and unchangeable was challenged in the eighteenth and nineteenth centuries by many people and, consequently, evolutionary change of life forms was accepted by quite a few thinkers and scientists by the time Darwin was writing his famous book. What set Darwin's work apart from the speculations of most previous writers was that he provided a more believable mechanism for the process of evolution, and that he marshalled a lot of evidence for evolution into a fairly coherent argument.

The mechanism of natural selection provided by Darwin (and independently, at the same time, by Alfred Russel Wallace) is at one level extremely simple, almost deceptively so. Later on, we will discuss the operation of natural selection in some detail. For the moment, I will just say that the unfortunate phrase “*survival*

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The unfortunate phrase “*survival of the fittest*” is not a good description of natural selection and has, in fact, led to much unnecessary debate.

A far better and equally concise definition of natural selection is “*heritable differential reproductive success*”.

“*of the fittest*” is not a good description of natural selection and has, in fact, led to much unnecessary debate (interestingly, the phrase itself is not Darwin’s: it was coined by Herbert Spencer). A far better and equally concise definition of natural selection is “*heritable differential reproductive success*”. Darwin’s argument for natural selection was built up by analogy to what happens when an animal breeder tries to develop a variety of any species that has certain desirable (according to the views of the breeder) characteristics.

Suppose a breeder wants to develop a breed of, say, pigeons with a long tail. The way in which this would be done would involve screening an available population for individual birds with longer than average tails, using them to breed from, and repeating this process over many generations – this is called artificial selection. After several generations of artificial selection, one ends up with a breed of pigeons that has an average tail length far greater than that in the original population. The efficacy of artificial selection was well appreciated in Darwin’s time and, indeed, the effectiveness of artificial selection underlies major advancements in agriculture. It is also intuitively obvious that there are two prerequisites for artificial selection to be effective in altering the characteristics of a population over time. First, there must exist variation for the trait that is going to be selected for in the population and, second, that variation must be heritable. If birds with longer tails are no more likely to have long tailed offspring than the average bird, then the process simply will not work.

What Darwin argued was that in any population of a species inhabiting a particular environment, there would be variation for some traits that would affect the ability of individuals to successfully make a living in that environment. By virtue of their traits, some individuals would be better able to survive and reproduce in that environment than others, and the traits that conferred upon them this greater *fitness* would, therefore, become more common in that population over many generations. It should be clear from this explanation that fitness in the Darwinian sense implies not physical prowess per se, but rather the ability, in the final ac-



counting, to produce offspring. Thus, whenever there exist heritable differences in reproductive success among individuals in a population, natural selection is, by definition, operating. Unlike in artificial selection, there is no *a priori* criterion for deciding who is to breed here: the environment imposes selection merely by being there and challenging the individual organisms to survive and reproduce in it.

Since those individuals who are better able to function in a given environment will be more successful than others in reproducing in that environment, natural selection will result in populations becoming better adapted to their environments. Similarly, since environments differ greatly, even populations of the same species that inhabit different regions may, in time, evolve to become quite different from each other. Over long periods, they may differentiate to such an extent that they can no longer interbreed and have, thus, effectively become different species. At the same time, sets of species descended relatively recently from a common ancestor will also share certain features in common, despite differing from one another in many ways. The idea of adaptive evolution through natural selection as developed independently by Darwin and Wallace, therefore, provided a plausible explanation for the adaptiveness, relatedness and diversity of species, thereby addressing the principal question that had faced biologists for many years.

There was, however, one fundamental problem with this explanation of adaptive evolution and this was recognized by Darwin. The problem was that of inheritance: if inheritance followed the blending pattern, as was commonly believed, then evolution by natural selection just would not work. The real issue here has to do with the prerequisites for selection (whether artificial or natural) to work – there must exist heritable variation for the relevant traits. Yet, one consequence of blending inheritance would be to homogenize the population. Imagine starting with several cans of white and black paint and mixing them up in pairs and pouring the resulting mixture into new sets of cans to generate the next generation. Pretty soon you will end up with many

Fitness in the Darwinian sense implies not physical prowess per se, but rather the ability, in the final accounting, to produce offspring. Thus, whenever there exist heritable differences in reproductive success among individuals in a population, natural selection is, by definition, operating.



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cans of grey paint and the population of paint cans will then be homogenous with regard to colour. Thus, the missing conceptual link in Darwin's theory was a mechanism of heredity that would somehow permit the maintenance of genetic variants in the population. In retrospect, it is clear that what was needed was a particulate theory of inheritance which, unknown to the world at large, Mendel's work had already provided. Darwin, realizing this problem, tried to develop a theory of inheritance that would maintain genetic variants but, as we realize today, his theory was just plain wrong. It is one of the great ironies of biological history that there exists no record of any scientific correspondence between Gregor Mendel and Charles Darwin, though the two pioneers were contemporaries.

The other great irony is that once Mendel's work was rediscovered and widely disseminated in the biological community, it was actually used for many years to deny the validity of Darwin's theory of evolution by natural selection. By the time Mendel's work was rediscovered, there was a well-established group of scientists in England who had been trying to understand the mechanisms of heredity by comparing the distributions and statistical relationships of metric traits (such as height, weight, yield, etc.) between parents and offspring. In the early 1900s, this group was headed by Pearson who strongly felt that it was variation in such metric or quantitative traits, as opposed to discrete traits such as flower colour, that was really important in evolution. Thus, when Mendel's work was rediscovered, Pearson and his group of Biometricians refused to accept Mendel's laws as being relevant to the inheritance of the quantitative traits that they felt were important in evolution. They argued that Mendel's laws were an oddity describing, perhaps, the inheritance of some discrete traits, but lacking general applicability and certainly irrelevant to understanding Darwinian evolution. On the other extreme of the debate were workers like de Vries, who argued that gradual variations such as those in metric traits studied by the Biometricians were irrelevant to evolution and that evolution, in fact, occurred through dramatic mutations that at one stroke



caused large phenotypic differences to arise between individuals. In fact, de Vries felt that his mutational theory of evolution obviated any need for natural selection to be invoked as a cause for evolutionary change and his theory was, thus, clearly anti-Darwinian. Many other Mendelians, like Bateson, while not subscribing to de Vries' extreme views, did nevertheless believe that since genetic change in Mendelian traits was clearly discontinuous, this somehow invalidated Darwin's idea of gradual evolution by the progressive accumulation of small differences over many generations. Of course, gradualism is conceptually not central to Darwin's idea but Darwin had stuck to it despite advice to the contrary from his friend T H Huxley who was also a great champion of Darwin's views. At that time, therefore, gradualism, as enshrined in the dictum '*natura non facit saltum*' (Nature does not make great leaps), was considered a critical component of the Darwinian theory of evolution.

It is hard to underestimate the importance of this schism between the Mendelians and the Biometricians in early twentieth century biology. No progress could be made in understanding the most fundamental biological phenomenon – that of evolution – until this gap was bridged. Finally, in 1918, R A Fisher showed that quantitative variation in metric traits was completely consistent with Mendelian inheritance by proposing that such traits are encoded by multiple genes and the unfortunate division between genetics and evolution thus came to a formal end. In fact, Fisher very clearly recognized the significance of Mendel's theory of particulate inheritance to the mechanism of evolution through natural selection and wrote in 1930: "*In the future, the revolutionary effect of Mendelism will be seen to flow from the particulate character of the hereditary elements. On this fact a rational theory of Natural Selection can be based, and it is, therefore, of enormous importance.....That an independent study of Natural Selection is now possible is principally due to the great advance which our generation has seen in the science of genetics.*"

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S S Chetverikov in the USSR laid the theoretical foundations of evolutionary genetics, thereby completing the synthesis of Mendelian and Darwinian ideas. In the 1940s, 1950s, and 1960s, the theoretical work of these intellectual giants in biology began to percolate down to experimentalists, largely spearheaded by the efforts of scientists like Dobzhansky and Ford and what has been described as the Great Synthesis (of genetics, palaeontology and ecology into an overarching theory of evolution) had begun. However, the foundation for the work of these giants was laid in 1908, with the independent publication by G H Hardy and Wilhelm Weinberg of a principle laying down the inertial state for the genetic composition of a population.

From Families to Populations: A Wider Stage for the Dance of the Genes

Very often in a well-choreographed dance sequence, the combination of a number of smaller groups of dancers performing fairly simple movements and steps together results in an extremely beautiful kaleidoscope of seemingly intricate patterns over the entire stage. We have seen so far the dance of the genes in small groups as they come together in pairs, recombine, assort into gametes, and come together again in zygotes within single lineages or families deriving from a pair of individuals in the parental generation. It is time, now, to widen our view a little and look at the whole stage, examining how genes in an entire population dance their way from one generation to the next, all the time remaining faithful to Mendel's Laws while moving from parents to gametes to offspring, and to gametes once again. We will try to see if a knowledge of Mendelian patterns of genetic transmission allows us to deduce population level patterns in the transmission of genes across generations.

In order to describe the transmission of genes within a family, we had to be able to characterize the parents in terms of their genotypes, and we saw how we could characterise the offspring in any particular generation in terms of phenotypic or genotypic ratios. Following the same logic, the genetic composition of a



population with regard to any particular locus at any generation can be described in terms of an array of genotypic frequencies. Consider a human population in which 1511 people have blood group M, 1719 have blood group N, and 2678 have blood group MN. The MN blood group system in humans is an example of codominance: the blood groups M, N, and MN correspond to the one locus genotypes *MM*, *NN*, and *MN*, respectively with neither allele being dominant. We can characterize the genetic composition of this population in two ways, in terms of either genotypic frequencies, or allele frequencies. The frequencies of the three genotypes can be easily calculated as the proportion of individuals of each genotype in the population as follows.

$$MM = 1511 / (1511 + 1719 + 2678) = 0.2557$$

$$NN = 1719 / (1511 + 1719 + 2678) = 0.2909$$

$$MN = 2678 / (1511 + 1719 + 2678) = 0.4534$$

To calculate the frequencies of the two alleles, we need to remember that each individual possesses two alleles, thus the total number of alleles in the population is twice the number of individuals. Similarly, we need to bear in mind that *MM* and *NN* individuals bear two copies of the same allele (they are called *homozygous*) whereas the *MN* individuals (*heterozygous*) have two different alleles at this locus. The allelic frequencies can, therefore, be calculated as follows.

$$M = ((2 \times 1511) + (1 \times 2678)) / (2 \times (1511 + 1719 + 2678)) = 0.4824$$

$$N = ((2 \times 1719) + (1 \times 2678)) / (2 \times (1511 + 1719 + 2678)) = 0.5176$$

The primary characterization of the genetic structure of a population is, of course, in terms of genotypic frequencies, because allelic frequencies are consequent upon and easily derived from the genotypic frequencies. In some situations, as we shall see later, the relationship is symmetric and we can infer genotypic frequencies from allelic frequencies. When this is possible, it makes our task easier because it is simpler to keep track of allele

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frequencies rather than genotypic frequencies simply because there are less of them. This may not seem to be a big deal for a one locus two allele system like the one we are discussing. However, many loci have a large number of possible alleles, even though any particular individual will only have two of them. For example, the ABO blood group locus in humans has three alleles – i^A , i^B and i^O . Consequently, there are six possible genotypes at this locus – $i^A i^A$, $i^A i^B$, $i^A i^O$, $i^B i^B$, $i^B i^O$, and $i^O i^O$.

In general, for a one locus system with m alleles ($A_1, A_2, A_3, \dots, A_m$, which can be written in convenient shorthand as alleles A_i , $i = 1 \dots m$), the number of possible genotypes is $m(m + 1)/2$. To see why this is so, consider the kinds of genotypes possible. Clearly, there are m different homozygous genotypes, corresponding to the m alleles. Now, in heterozygous individuals, each of these m alleles can be combined with each of the $m - 1$ others, yielding $m(m - 1)$ different heterozygotes. But here, we are considering *ordered heterozygotes* which means that we are distinguishing between genotypes $A_1 A_2$ and $A_2 A_1$, even though genetically speaking they are identical. So, considering *unordered heterozygotes* (treating genotypes $A_1 A_2$ and $A_2 A_1$ as identical), we actually have only half the number of possible genotypes, implying that the number of heterozygous genotypes in an m allele system is $m(m - 1)/2$. The total number of genotypes is, therefore, $m + m(m - 1)/2$, which is easily simplified as $m + m(m - 1)/2 = (2m + m^2 - m)/2 = (m^2 + m)/2 = m(1 + m)/2$. Thus, as the number of alleles increases, the number of genotypes that need to be kept track of increases even more rapidly. With two loci, the situation gets worse: a two locus system with only two alleles per locus requires the frequencies of ten different genotypes to be described. Thus, one of our first concerns in understanding any population genetic situation is typically whether a description of the genetic composition of the population in terms of allelic – or for two locus systems, gametic – frequencies will suffice.

Now that we have discussed how the genetic composition of a population can be described and quantified, let us introduce some notation which we will be using. Different alleles at a locus, A ,



will be described as A_i ($i = 1 \dots m$), and the allele frequency of A_i will be depicted by a lower case letter with the appropriate subscript, typically p_i ($i = 1 \dots m$). Ordered genotypic frequencies will be depicted with upper case letters, such that P_{ij} will refer to the frequency of the genotype A_iA_j , and P_{ji} to that of A_jA_i (the overall, or unordered frequency of A_iA_j heterozygotes is, consequently, depicted by $2P_{ij}$). Clearly, frequencies, being proportions, must sum to one; that is, $\sum_{i,j=1}^m P_{ij} = 1$, and $\sum_{i=1}^m p_i = 1$. The relationship between allelic and genotypic frequencies that we discussed earlier can now be succinctly described as $p_i = \sum_{j=1}^m P_{ij}$.

One Way to Follow the Dance of Genes: Mating Frequencies

Let us now try to follow genes as they move from one generation to the next. Imagine there is a large population of 10,000 mice with differing coat colour based upon their genotype at a codominant biallelic locus. 900 mice have black coats (A_1A_1), 4900 have white coats (A_2A_2) and 4200 have grey coats (A_1A_2). The genotypic frequencies are, thus, $P_{11} = 0.09$, $2P_{12} = 0.42$ and $P_{22} = 0.49$, and the allelic frequencies are $p_1 = \sum_{j=1}^2 P_{1j} = P_{11} + \frac{1}{2} 2P_{12} = 0.09 + 0.21 = 0.3$, and $p_2 = 1 - p_1 = 0.7$ ($p_2 = 1 - p_1$ because there are only two allelic frequencies and they must sum to 1). Now assume that no new mutations occur, no individuals move into or out of the population, coat colour is unrelated to the fertility of individuals and the survival of their offspring to adulthood, and that these mice mate at random with regard to coat colour. The significance of these assumptions will be discussed at length later; for the time being, just assume them. The question now is: can we use our knowledge of Mendel's Laws to deduce what the genetic composition of the population would be in the next generation with regard to allelic and genotypic frequencies at the coat colour locus? The answer is yes.

Can we use our knowledge of Mendel's Laws to deduce what the genetic composition of the population would be in the next generation with regard to allelic and genotypic frequencies at the coat colour locus? The answer is 'yes'.



We can begin by trying to quantify the different types of matings that are possible between individuals of different coat colour genotypes. Under the assumption of random mating (unless explicitly specified, the phrase random mating will always be used in the sense of random mating with regard to the locus or loci under consideration), the proportion of matings between different genotypes can be seen to be the product of the respective genotypic proportions. Consequently, matings between two A_1A_1 individuals as a proportion of the total number of matings occurring in the population will be $P_{11}^2 = (0.09)^2 = 0.0089$, or 0.89%. Matings between an A_1A_1 and an A_2A_2 individual can occur in two different ways, depending on whether the A_1A_1 individual is male or vice versa, with each type of mating occurring with frequency $P_{11}P_{22}$, yielding a total frequency for $A_1A_1 \times A_2A_2$ matings of $2P_{11}P_{22} = 2 \times 0.09 \times 0.49 = 0.0882$, or 8.82%. In this manner, we can calculate the frequency of each type of mating, and can then apply Mendel's Laws to predict the proportions of different genotypes among the progeny of each type of mating (*Table 3*). Note that the frequencies in column two of *Table 3* sum up to one, as do those in column three. To obtain the genotypic frequencies in the next generation, all we need to do is to sum up the offspring frequencies from column three of *Table 3* separately for each genotype, as follows (P'_{ij} refers to P_{ij} in the next generation, a convention we will follow for both allelic and genotypic frequencies).

$$P'_{11} = 0.0081 + 0.0378 + 0.441 = 0.09$$

$$P'_{12} = 0.0378 + 0.0882 + 0.0882 + 0.2058 = 0.42$$

$$P'_{22} = 0.0441 + 0.2058 + 0.2401 = 0.49$$

In other words, the frequencies of the three genotypes (and, consequently, the alleles as well) have not changed from what they were in the previous generation and are at equilibrium. This is an interesting observation and, of course, we now have to decide whether this is a unique consequence of the particular genotypic frequencies we chose, or a more generally applicable result. We shall explore this issue in detail in Part 2 of this article.



Type of Mating	Frequency	Offspring Frequencies		
$A_1A_1 \times A_1A_1$	$P_{11}^2 = 0.0081$	A_1A_1 0.0081	A_1A_2 0.0	A_2A_2 0.0
$A_1A_1 \times A_1A_2$	$4P_{11}P_{12} = 0.0756$	A_1A_1 0.0378	A_1A_2 0.0378	A_2A_2 0.0
$A_1A_1 \times A_2A_2$	$2P_{11}P_{22} = 0.0882$	A_1A_1 0.0	A_1A_2 0.0882	A_2A_2 0.0
$A_1A_2 \times A_1A_2$	$4P_{12}^2 = 0.1764$	A_1A_1 0.0441	A_1A_2 0.0882	A_2A_2 0.0441
$A_1A_2 \times A_2A_2$	$4P_{12}P_{22} = 0.4116$	A_1A_1 0.0	A_1A_2 0.2058	A_2A_2 0.2058
$A_2A_2 \times A_2A_2$	$P_{22}^2 = 0.2401$	A_1A_1 0.0	A_1A_2 0.0	A_2A_2 0.2401

Table 3. The frequencies of different possible types of matings among mice with different coat colour genotypes, along with the types of offspring that each mating will produce, and the proportion of each type of offspring with respect to the total offspring population resulting from all matings. For example, an $A_1A_1 \times A_1A_2$ mating will produce 50% A_1A_1 offspring and 50% A_1A_2 offspring, and this type of mating occurs with a frequency of 0.0756 in the population. Therefore, the proportion of each of the two genotypes of offspring resulting from this mating among the total number of offspring in the next generation will be $0.5 \times 0.0756 = 0.0378$.

It would also be obvious that tracking all the offspring from each type of mating is a fairly cumbersome task. We shall, therefore, also try to see if there are cleaner and simpler ways of tracking the genetic composition of a population from one generation to the next.

Suggested Reading

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