Mathematics and Biosciences in Interaction

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The Mathematics of Darwin's Legacy

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To Alice, who was born together with the idea of this book; and Renata, without whom neither would be possible (*FACCC*).

To Mafalda and Francisco, who are beginning to read while this book appears (*JFR*).

Contents

Preface

Fabio A.C.C. Chalub and José Francisco Rodrigues

The year 2009 had two important scientific celebrations: "The International Year of Astronomy" and the "Darwin Year". In Astronomy, four hundred years had passed since the first use of the telescope by Galileo Galilei and publication of the first two planetary laws by Johannes Kepler in the book Astronomia nova, published in Prague in 1609. In Biology, the bicentennial of Darwin's birthday and the sesquicentennial of the publication of his book *The Origin of Species*, published in London in 1859, are two important ephemerides of what is now commonly known as the theory of evolution [1]. However, 1809 was also the year of publication in Paris of the book *Philosophie zoologique*, by Jean-Baptiste Lamarck [2], containing an outline of the theory of evolution, although without the key concept of natural selection that was proposed later by Charles Darwin and, independently, by Alfred Russell Wallace.

Darwin's classical book had the great merit of showing that the organization and functionality of living beings comprise a natural process that Science can explain, but which in no sense had a single mathematical model. Nothing vaguely similar to an equation appears on any page. But Darwin respected mathematicians and even once said "I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics; for men thus endowed seem to have an extra sense" (quoted in [3]).

Also around one and a half centuries ago, Gregor Mendel, an Austrian monk and scientist, was studying the reproduction of peas in Brno, a city that is now in the Czech Republic. His work, in which statistics played a central role in predicting how traits were inherited from one generation to the next, led to the formulation of what later became known as Mendel's Laws of Inheritance, which were published in 1866 [4] but were rediscovered only at the beginning of the 20th century. What Mendel devised was the "mechanism of heredity" that was lacking in Darwin's theory. Until then, it was assumed that offspring were a blending of their progenitors. This would make evolution impossible, as variation would very quickly disappear from any population. This was a fundamental objection to Darwin's theory and, as it was only lately recognized, Mendel's laws formed not only the foundation of the modern science of genetics but also found the missing link that made the theory

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of evolution a mature one, since it is a key ingredient for differential reproduction and, therefore, selection and evolution.

The so-called "Modern Evolutionary Synthesis", made possible only by the active intervention of a generation of great biologists with fundamental training in mathematics and physics, like Ronald A. Fisher, John Haldane, and Sewall Wright, among others, succeeded in merging Darwinian evolution and Mendelian genetics. In fact, the need to make the theory of evolution by natural selection explicitly quantitative was advocated by British biometricians, with the development of statistics as an area of mathematical enquiry, that led to creation of the journal *Biometrika*, by Pearson, Weldon and Galton (cousin of Darwin) in 1901. But that synthesis, in which the fundamental concepts of evolution, selection and mutation were formulated in terms of a mathematical model, took place only in the 1920s and 1930s. An important development in biological modelling with a strong mathematical background that is also worth mentioning was the formulation of a neutral theory of evolution, by Motoo Kimura [5] in the 1960s, in which the vast majority of evolutionary change at the molecular level is caused by random drift of selectively neutral mutants. A second important development was the introduction of evolutionary game theory in Biology, by John Maynard Smith [6] in the mid-1970s, in which the replicator and the replicator-mutator equations play a fundamental role, in particular, giving origin to "Darwinian Dynamics" or "Evolutionary Dynamics" as a mathematical description of the dynamical process of variability, heritability and the struggle to survive and reproduce that underlies natural selection [3, 7].

This briefly sketched story, is, in a certain sense, the starting point of this book; however, this was not the starting point of the relationship between mathematics and biology nor does it cover the whole field of Mathematical Biology, which includes many topics such as population dynamics, theoretical ecology, epidemiology, population genetics, theoretical immunology, neural networks, pattern formation, and genomic or proteomic analysis. That story is in fact much older. However, it is difficult to establish the beginning of this interaction. One of the first references is from the 13th century, when Fibonacci's rabbit problem was formulated in 1202: "Suppose a newly-born pair of rabbits, one male, one female, are put in a field. Suppose that our rabbits never die and that after the first month, females always produce one new pair (one male, one female) every month from the second month on. How many pairs of rabbits will there be after a certain number of months?" The assumptions are so unrealistic that this problem hardly can be considered a problem in biomathematics; actually, it appears as an interesting example of certain mathematical recursion [8]; however, the Fibonacci sequence plays an increasing role in the description of nature.

Despite the fact that Darwin was influenced by Thomas Malthus' "An Essay on the Principle of Population", first published in London in 1798, the model of population growth following a geometric progression was already well known by the mathematician Leonhard Euler. Already in the 18th century he discussed several examples of dynamics of human population and he understood that they

correspond to a model of exponential growth [9, 10]. Working with this model, he was able to observe, fifty years before Malthus, that a single couple, living only several hundreds of years ago, was able not only to generate all the human population at the 18th century but also, continuing with the same growth, even to attain so large a total population that the whole Earth could not be fed. He also contributed a chapter to a second edition of a first treatise on demography published in Berlin in 1761.

In an important memoir presented to the Academy of Science of Paris in 1760, Daniel Bernoulli made what is possibly the first use of modern mathematical techniques to solve a biologically relevant problem: the dynamics of smallpox. Bernoulli was ahead of modern epidemiology and divided the population into two categories: the susceptible and the immune (the survivors gain life-time immunity); these groups were modelled using differential equations. In fact, in his model he obtains and solves what we nowadays call a "logistic equation", which is a particular case of Bernoulli's differential equation, named after his uncle Jakob, who discussed it in 1695. Looking at the stationary states of these equations, he was able to project the loss in life-expectancy due to the disease. This had impact in the insurance market, and was also a central question in the introduction of inoculation in France [11].

Population dynamics is one of the most important fields of biomathematics; almost all books on the subject start with a chapter on that topic. We still call "Leslie matrices" the one introduced in the study of structured populations, despite the fact that they have no special attributes from the mathematical point of view [12]. The same thing happens with the (sometimes called) Verhust equation [13], which is just the logistic differential equation already considered and solved by the Bernoullis and is one of the simplest examples of a dynamical system. Perhaps the same cannot be said about the Lotka-Volterra equations, introduced almost simultaneously in 1925 and 1926, respectively, by the American statistician A.J. Lotka and the Italian mathematician Vito Volterra, that describe the interaction between different species and gave rise to a turning-point in mathematical biology in the 20th century, [14]. Other interesting facts with historical references to the interactions between mathematics and biology can be found in [15].

The first mathematical result of interest in evolution and genetics appeared only decades after Darwin. In the first decade of the 20th century, independently, the British mathematician G.H. Hardy [16] and the German doctor W. Weinberg [17] explained why recessive genotypes do not disappear. More precisely, they gave sufficient conditions to make gene frequencies static from one generation to the next. In their ideal model, an equilibrium is attained in a single generation. The knowledge of equilibrium is the baseline against which we can measure change, and evolution is ultimately a theory of (gene frequency) change. Their conditions were no-mutation, no-selection, no-migration, random mating, infinite population. The violation of any of these conditions could, on its own, be responsible for evolution.

Later on, R. Fisher [18] went further and quantified the change, pronouncing what is currently known as "the fundamental theorem of evolution": the rate of

change of the mean fitness of a population is equal to the fitness variance at each point in time. This will be discussed in detail in the chapters of this book written by W. Ewens, P. Schuster, and R. Burger. These first three papers will provide the reader with a broad and deep view of models in population genetics.

The book continues with a chapter by P. Jagers studying models for extinction. The starting point will be the Galton-Watson process, initially introduced in the study of extinction of family names. This shows (if someone is not yet convinced) the unifying nature of mathematical knowledge. P. Taylor presents the relations between group theory and homogeneous populations. This provides a consistent framework for generalisation to an entire population of results obtained by studying only one or a few (focal) individuals. Taylor finishes his chapter with a model of altruistic behaviour. This is the starting point of the following chapter, by J. Pacheco, where evolutionary game theory is intensively used to model collective action (in particular, cooperation). Solutions of social dilemmas are probably one of the most important problems we have to face in our daily life.

Yet, there are many different ways to study the evolution of cooperation; two important ones are kin selection and group selection. These models are reviewed and used in V. Jansen's chapter to provide a full understanding of the social behaviour of mice living in haystacks. When different individuals in the same population find different solutions to the same dilemma, we are possibly facing one of the most important problems in evolution: the concept of speciation. So important that the title of Darwin's masterpiece refers directly to it. This is the subject of the chapter by S. Mirrahimi, B. Perthame, E. Bouin and P. Millien and also of S. Méléard's chapter. Models for evolutionary branching, a more general concept, are studied from many different points of view: differential equations, integro-differential equations, stochastic modelling, individual-based models, asymptotic limits... all approaches unified by the concept of "adaptive evolution".

"Adaptive evolution" is also the topic of the last two chapters, respectively, by H. Metz and by M. Gyllenberg, H. Metz and R. Service. These chapters are primarily devoted to meso-evolution, where the focus is the change of traits of individuals in a population. A natural sequel to Metz's chapter, where some elements of an adaptive evolution theory are developed, this final chapter investigates how optimisation approaches fit that point of view.

The book ends with a large and extensive but not exhaustive, bibliography, a merging of all citations that appear in the book. At a first glance, this allows us a rather reasonable overview of the biomathematical literature in the last 150 years. We intend this book to be also a good starting point for anyone interested in working in biomathematics, especially in evolution.

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where the conference took place in November 2009, to reunite the scientific and logistic conditions that made this book possible.

Finally we conclude this introduction by adopting Metz's closing sentence and inviting you, interested reader, to join this hard and challenging task of bringing Biology and Mathematics closer and to contribute to the fruitful development of biomathematics!

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What Changes Has Mathematics Made to the Darwinian Theory?

Warren J. Ewens

Abstract. Mathematics has played a key role in validating the Darwinian theory of evolution by natural selection. Perhaps most importantly it shows that the variation needed for evolution by natural selection is conserved under the Mendelian evolutionary system. It then quantifies the rate at which favorable new genetic types are incorporated into a population by natural selection. Analyses at the whole genome level (the current active area of genetical research) are possible only by the use of mathematics, particularly the use of matrix theory. Finally, it is only by a mathematical analysis, using stochastic process theory, that the effects of random changes in gene frequencies, unavoidable because of the finite size of any population, can be assessed.

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1. Introduction

This chapter has three aims. The first is to give a brief introduction to the history of the Darwinian theory preceding the re-discovery of Mendelian genetics in 1900, with an emphasis on the problems that the theory encountered. It will be shown that these problems are resolved by mathematical methods based on the recognition of the Mendelian hereditary system. This leads to the second aim, which is to give a brief review of the fundamentals of genetics and a description of the Darwinian theory in Mendelian terms. The third aim, by far the most important one, is to give examples of cases where a mathematical approach was central to a formulation the Darwinian theory in genetical terms, resolves problems with that theory which were recognized from the earliest times, as well as fleshes out the theory in a way that would not be possible without mathematics. These aims also form the background to further mathematical analysis of the evolutionary process and current research activities to be found in other chapters of this book.

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2. Pre-Mendelian evolutionary theory

Various evolutionary principles and theories were advanced before Darwin's time, but here we consider only his theory of evolution by the action of natural selection, the only evolutionary principle to have survived critical examination. Darwin's theory was put forward in his monumental book [1], now generally called *On the Origin of Species*. The great paradox concerning his theory was that when the book appeared, in 1859, the nature of the hereditary mechanism was unknown, so that Darwin advanced the theory without any knowledge of this essential core element to any evolutionary theory. Worse than this, the prevailing theory of heredity when his book was published, and indeed for more than forty years afterward, was that any particular character in a child, for example the child's blood pressure, is in some sense more or less the average of the blood pressures of the two parents of that child. It is clear under this theory, the so-called "blending" theory of inheritance, that under random mating in the population the variance in blood pressure between individuals would halve in every generation, so that in a comparatively short number of generations all individuals in the population of interest would have essentially the same blood pressure. There would then be no variation for natural selection to act on. Of course we do not observe such uniformity in the present human population, so further argument is needed. Since variation in blood pressure to the degree that is actually observed would only arise from further factors of strong effect which cause the blood pressure of a child to deviate from the average of the blood pressures of the child's parents, the principle that selectively favored parents produce offspring who closely resemble them and thus are themselves selectively favored cannot be sustained. Darwin recognized that the blending theory of inheritance was a major problem for his theory, indeed *the* major problem, and because of this he unfortunately altered subsequent editions of his book in such a way as to substantially alter his theory.

This problem was not resolved until the rediscovery of the Mendelian hereditary mechanism [2] in 1900. A mathematical analysis based on this mechanism leads to the so-called Hardy-Weinberg law [3, 4] described later, and this law shows that there is no intrinsic tendency under Mendelian inheritance for variation (in this case genetic variation) to be lost: once established it stays unchanged (unless forces like selection act, a matter discussed further below). It is the quantal nature of the gene, passed on as a discrete entity from parent to offspring, that resolves Darwin's problem, so that there is no blending involved. It is a pity that Mendel's 1866 paper, although evidently sent to Darwin, was not recognized by him or by anyone else for the revolutionary document that it indeed was.

3. The basics of Mendelism

Genetics is an extremely complex subject, and any attempt to describe it briefly must involve severe simplification, sometimes to the extent of introducing minor distortions from reality. It is sufficient for our immediate purposes to say that genes

lie on chromosomes, which are thread-like objects in the cells of any organism. Interest lies mainly in *diploid* organisms, such as humans, who obtain genetic material from two parents, and we consider here only this case. In the case of humans, leaving aside the sex chromosomes (which are XX for females, XY for males), each individual carries 22 pairs of chromosomes, one member of each pair coming from that individual's mother and the other from the father. (In other diploid species numbers different from 22 arise.) We may regard the genes as being like beads on the chromosome "threads". These genes lie at particular positions, or loci, so that at any locus any individual has two genes, one on each of the two chromosomes.

We consider for the moment some specific locus. Genes at this locus are of one or other *allelic type*. For example, at the well-known ABO blood group locus, there are three possible allelic types, or *alleles*, A, B and O, and since any individual carries two genes at this locus, one maternally and one paternally derived, each individual must be either AA, AB, AO, BB, BO or OO. We say that these are the six possible *genotypes* at this locus.

It is important to distinguish between the genotype and the *phenotype* of any individual. In the case of the ABO system, both A and B are *dominant* to O, which implies that the outward appearances of AA and AO individuals are the same, as are the outward appearances of BB and BO individuals. Thus there are only four possible phenotypes at this locus, called A (for AA and AO genotypes), B (for BB and BO genotypes), AB (for AB genotypes) and O (for OO genotypes).

The ABO notation is specific to the ABO gene locus, and to consider the general case it is necessary to introduce a more flexible notation. If there are k possible alleles at some locus A, they are generically denoted here by $A_1, A_2, \ldots, A_k$. These k alleles define $k(k+1)/2$ possible genotypes, $A_1A_1, A_1A_2, \ldots, A_1A_k, A_2A_2, \ldots, A_{k-1}A_k$, A_kA_k. The theory outlined below uses this generic notation.

With this background in place we turn now to evolutionary questions. The genotype frequencies in any daughter generation depend on the mating scheme adopted by the parental generation. We assume initially that random mating applies. Suppose also for the moment that there is no selection, so that the fitness of any individual is independent of his genotype. We also assume no mutation or any other disturbing force. Suppose then that in the parental generation the frequency of the genotype is P_{ii} and of the genotype A_iA_j (for $i \neq j$) is $2P_{ij}$. (It is convenient to describe P_{ij} as the frequency of the *ordered* genotype A_iA_j.) The frequency p_i of the allele A_i is, clearly,

$$p_i = \sum_{j=1}^{k} P_{ij}. \tag{3.1}$$

The Hardy-Weinberg law follows immediately from this. It states that in the daughter generation at the time of its conception the frequency of the genotype A_iA_i is p_i^2 and that of the genotype A_iA_j $(i \neq j)$ is $2p_ip_j$. (If mating is not at random, these values no longer apply. The non-random-mating case is considered below.) Elementary calculations show that the frequency of A_i is p_i, the same value

as that applying in the parental generation, and also that the daughter generation genotype frequencies and thus the frequency of the every allele remains unchanged in all future generations. This observation validates the "preservation of variation" comment made in Section 2. Of course, mutation and selection change allelic frequencies from one generation to the next, and random changes will also arise by random sampling, since all populations are finite. Nevertheless all these changes are generally small, and the central importance of the preservation of variation concept remains unaltered.

The Hardy-Weinberg law does not apply under non-random mating, for example under assortative mating (the tendency of like to mate with like). Nevertheless, one important mathematically-derived conclusion applies whatever the form of mating, namely that, again assuming no selection, mutation, or any other disturbing force, allelic frequencies remain unchanged from one generation to the next. This is not true of genotype frequencies, which often change from one generation to the next under non-random mating. While this observation does have some important consequences, the essential feature of the preservation of allelic frequencies, and in this sense of genetic variation, remains. Mendelism is an intrinsically variation-preserving hereditary mechanism.

We now consider the evolutionary process further, introducing complications such as selection and mutation. Suppose first that the fitness of any individual depends only on the genes that he carries at some locus A, at which only two alleles can occur, A_1 and A_2. (By fitness here we mean viability fitness, that is the capacity to survive from conception to reproduction. Fitnesses involving mating success and fertility lead to complicated algebra that we do not go into here.) Denote the fitnesses of the three genotypes A_1A_1, A_1A_2 and A_2A_2 by w_{11}, w_{12} and w_{22} respectively. We assume random mating, so that the frequencies of these three genotypes at the time of conception of any generation are $p^2, 2p(1-p)$ and $(1-p)^2$ respectively, where the frequency of A_1 is p at this time. The so-called *mean fitness* $\overline{w}$ of the population at this time, calculated in the standard statistical fashion for a mean, is given by

$$\overline{w} = p^2 w_{11} + 2p(1-p)w_{12} + (1-p)^2 w_{22}. \tag{3.2}$$

If p' is the frequency of A_1 at the time of conception of the next generation, elementary calculations show that

$$p' = p + \frac{p(1-p)}{\overline{w}} \left\{ w_{11}p + w_{12}(1-2p) - w_{22}(1-p) \right\}. \tag{3.3}$$

This equation can be used to describe the fundamental micro-evolutionary process, which is the replacement of a "less fit" allele in a population by a "more fit" allele. It can also be used to explain the often observed "standing genetic variation", as is shown later.

Equation (3.3) shows that only the relative (rather than the absolute) values of the w_{ij} are necessary to describe this micro-evolutionary process, and thus we are free to choose one of the three fitnesses to take the value 1. In the case where

$w_{11} > w_{12} > w_{22},$, so that A_1 is the "more fit" allele, it is convenient to write $w_{11} = 1 + s, w_{12} = 1 + sh, w_{22} = 1$, where $s > sh > 0$. We generally think of the case where s is small, perhaps of order 1%. In this case equation (3.3) shows that, to a close approximation,

$$p' - p = sp(1-p)\{p + h(1-2p)\}. \tag{3.4}$$

If unit time corresponds to one generation, this in turn can be approximated by

$$\frac{\mathrm{d}p}{\mathrm{d}t} = sp(1-p)\{p + h(1-2p\}. \tag{3.5}$$

This equation is easily solved, and the solution provides the trajectory of the increase in the frequency of A_1 over time. It is perhaps more useful to calculate the time $t(p_1, p_2)$ required for this frequency to increase from some value p_1 to some larger value p_2. Clearly

$$t(p_1, p_2) = \int_{p_1}^{p_2} [sp(1-p)\{p + h(1-2p\}]^{-1}\mathrm{d}p. \tag{3.6}$$

Many conclusions can be found from these simple formulae, especially the slow rate of change in the frequency of A_1 when this frequency is either large or small. A collection of results arising from (3.6) and from similar but more complex equations was found by Haldane in the 1920's, and summarized in [5]. These equations bear some similarity to corresponding equations in physics, in that they allow one to predict the future evolution of a system, given the appropriate parameter values and the current state of that system.

An empirical confirmation of equation (3.5) arises in describing the evolution of the melanic form of the peppered moth *Biston betularia* during the 19^{th} century in England. Originally the pale form of this moth was prevalent, but with the rise of industrial pollution and the consequent darkening of the bark of the trees on which these moths settled, the melanic form became selectively favored since it became increasingly difficult for predators to observe the dark form on these trees. Empirical estimates of the selective values s and h were made and it was found that the trajectory of the frequency of the melanic form closely followed that predicted by equation (3.5).

In the case where the heterozygote is the most fit genotype, so that $w_{11} < w_{12} > w_{22}$, there is a point of stable equilibrium where the frequency p^* of A_1 is

$$p^* = \frac{w_{12} - w_{22}}{2w_{12} - w_{11} - w_{22}}. \tag{3.7}$$

This is the case of "heterozygote selective advantage", observed often in reality, and thus this fitness configuration is sufficient to explain the observation of standing genetic variation. (When $w_{11} > w_{12} < w_{22}$ there is an equilibrium frequency again at the same value p^*, but this equilibrium is unstable and thus of little interest.) Thus the Mendelian system can explain not only evolution (in the sense of changes in allelic frequencies) but also the existence of standing genetic variation.

So far we have not considered the possibility of mutation. Genes mutate (usually at a very low rate, of order 10^{-5} or 10^{-6}), so that for some purposes mutation can be ignored. On the other hand mutation eventually is the source of all genetic variation, so that despite these low rates a complete analysis of the evolutionary process must allow for mutational events. Here we assume that an A_1 gene mutates to an A_2 gene with probability u, while an A_2 gene mutates to an A_1 gene with probability v. In the case where there is no selection there is a stable equilibrium of allelic frequencies where the frequency of A_1 is $v/(u+v)$. The case where selection and mutation both arise is of course also of interest. In the case of heterozygote selective advantage there is a stable equilibrium close to that value given in equation (3.7), assuming that selective differences are substantially higher than the mutation rates. The case where $w_{11} > w_{12} > w_{22}$ is perhaps of more interest. Here there is a stable equilibrium frequency of A_1 just less than 1. This situation is relevant when A_2 is a disease allele that is maintained at a low frequency in a population because of recurrent mutation from A_1 to A_2, and is much studied in disease genetics applications.

The above calculations assume only two possible alleles at the locus of interest, and also assume random mating. It is possible to generalize these calculations to allow any number of alleles at the locus and any form of mating, although the analysis becomes more complex. Suppose then that the (viability) fitness of any individual depends only on his genotype at some gene locus A, at which alleles $A_1, A_2, \ldots, A_k$ can arise, and denote the fitness of an individual of genotype A_iA_j by w_{ij}. Consider some parental population at its time of conception, with its genotype frequencies at this time being given as above equation (3.1). These genotype frequencies are not necessarily assumed to be in Hardy-Weinberg form, so that it is not necessarily assumed that $P_{ii} = p_i^2$ and that $P_{ij} = p_ip_j$, since random mating in the preceding generation is not necessarily assumed. The mean population fitness $\overline{w}$ of the population in this generation at the time of its conception is

$$\overline{w} = \sum_i \sum_j P_{ij} w_{ij}. \tag{3.8}$$

Straightforward calculations show that the frequency p_i' of A_i at the time of reproduction of the individuals in the parental generation is

$$p_i' = \frac{1}{\overline{w}} \sum_j P_{ij} w_{ij}. \tag{3.9}$$

Under any form of mating (for example random mating, selfing, partial selfing, assortative mating), p_i' is also the frequency of A_i in the daughter generation at its time of conception. In other words, equation (3.9) can be taken as providing the frequency of A_i in the daughter generation at the time of conception, and this is the interpretation that is normally placed on this equation. It is one component of the full evolutionary description of the changes over one generation of the frequencies of the various genotypes at this locus.

It is not possible to calculate the daughter generation genotype frequencies without knowledge of the mating scheme. This in turn implies that gene frequencies beyond the daughter generation cannot be calculated from genotype frequencies in the parental generation without knowledge of the mating scheme, and thus we are unable to track gene frequency evolution over more than one generation without this knowledge. On the other hand, if random mating can be assumed over all successive generations, this tracking can be carried out.

It was noted above that, in the case where two alleles only are possible at the locus, there will be a point of stable equilibrium with both alleles present at positive frequency if the heterozygote has a higher fitness than does either homozygote. The condition for such an equilibrium when there are k possible alleles at the locus, even assuming random mating, is far more complex. We define an internal equilibrium to arise if all alleles have a positive frequency at that equilibrium. Then the necessary and sufficient condition that there exist an admissible stable equilibrium is that the matrix W, whose typical element is w_{ij}, has exactly one positive eigenvalue and at least one negative eigenvalue, as shown by Kingman [6]. In this case the population evolves from any initial set of allelic frequencies at which all alleles have positive frequency to this equilibrium.

A simple example of this case arises when all heterozygotes $A_iA_j, (i \neq j)$ have fitness 1 and all homozygotes $A_iA_i, (i = 1, 2, \ldots, k)$ have fitness $1 - s$, where $1 > s > 0$. In this case it is easily shown that the eigenvalues of the matrix W are $k - s$ (with multiplicity 1) and $-s$ (with multiplicity $k - 1$). These eigenvalues satisfy the condition of the previous paragraph, and (as expected from symmetry arguments) the population evolves to a stable equilibrium where all alleles have frequency k^{-1}.

If there is no admissible stable equilibrium the evolutionary behavior is much more complicated. One useful result of Kingman [6] is that if W has j positive eigenvalues, at most $k-j+1$ alleles can exist at an admissible stable equilibrium. If all allelic frequencies are initially positive, the frequencies of the remaining alleles will approach zero over time under the action of natural selection. Clearly these conclusions can be reached only by a mathematical analysis.

4. Evolutionary principles deriving from a mathematical approach

4.1. The problem

There is a serious problem in evolutionary theory arising from the fact that the fitness of any individual depends on all the genes in his genome, whereas each parent passes on only half of his genes to a child. (Complications due to the sex chromosome are ignored here.) The Darwinian theory is based on the idea that a more "fit" individual leaves, on average, more offspring than a less fit individual, and that the offspring of the more fit individuals in a population inherit this increased fitness from their parents, leading to an increased population frequency of the more fit types. But if a parent only passes on half of his/her genes to an

offspring the offspring only partially resembles the parent, and there has to be some modification to the Darwinian theory.

This problem has to be resolved by mathematical methods, and the initial step in making this modification is to introduce the concept of the "fitness" of any allele. This has to be a theoretical, or mathematical, construct, since an allele does not have, in reality, a fitness. Despite this fact, this construct is of the utmost importance, and leads to significant insights into the properties of the evolutionary process under Mendelian inheritance. We now introduce this allelic "fitness" concept in the case of a general number k of alleles at the gene locus of interest.

The concept of "allelic fitnesses" of the alleles $A_i, (i = 1, 2, \ldots, k)$ derives from the concept their average effects. These are defined, respectively for these alleles, as the values of $\beta_1, \beta_2, \ldots, \beta_k$ which minimize the quantity

$$\sum_i \sum_j P_{ij}(w_{ij} - \beta_i - \beta_j)^2. \tag{4.1}$$

This minimization procedure is in effect an attempt to fit the various genotype fitnesses by the sum of two values, each of the two values corresponding to the two alleles in the corresponding genotype. The motivation for this is that, as discussed above, a parent passes on one of the two genes that he has at any gene locus to an offspring, and the minimization procedure leads to a "fitness" $\beta_i + \beta_j$ for an individual of genotype A_iA_j. The values of $\beta_1, \beta_2, \ldots, \beta_k$ found from this weighted least-squares procedure are the solutions of the equations

$$p_i\beta_i + \sum_j P_{ij}\beta_j = \sum_j P_{ij}w_{ij}, \quad (i = 1, 2, \ldots, k). \tag{4.2}$$

Equation (3.9) shows that this equation can be written equivalently as

$$p_i\beta_i + \sum_j P_{ij}\beta_j = \overline{w}p_i', \quad (i = 1, 2, \ldots, k). \tag{4.3}$$

In general the solution (for $\beta_1, \beta_2, \ldots, \beta_k$) of these equations cannot be written down explicitly. Summation over all alleles in (4.3) leads to the equation

$$2\sum_i p_i\beta_i = \overline{w}. \tag{4.4}$$

This equation confirms that we may regard the "fitness" of the genotype A_iA_i as being $2\beta_i$ and the "fitness contribution" of the allele A_i as being β_i. It also shows that the population mean fitness can be calculated as a weighted sum these allelic "fitness contributions", the weights being the frequencies of the respective alleles.

The sum of squares removed by fitting the values of $\beta_1, \beta_2, \ldots, \beta_k$ in (4.1) is the so-called (single locus) additive genetic variance in fitness, denoted by σ^2_{A}. It is of the utmost importance, and is that component of the total variance $\sigma^2 = \sum_i \sum_j P_{ij}(w_{ij} - \overline{w})^2$ in fitness that is explained by genes within genotypes, and is thus often called in the modern literature the "genic" variance. (In view of the fact that an additivity assumption is made in the least-squares procedure, with the "fitness" of the genotype A_iA_j being thought of as $\beta_i + \beta_j$, it might best be

called the "additive genic" or "additive allelic" variance.) If values w_i and w_j exist such that, for all (i, j), the fitness w_{ij} can be computed as $w_i + w_j$, then $\beta_i = w_i$ and σ^2_{A} is equal to the total variance in fitness. If no such values exist there exists "dominance", or non-additivity, among the fitness values, and this leads to the concept of a non-additive or dominance variance σ^2_{D}, defined simply as $\sigma^2 - \sigma^2_{\mathrm{A}}$.

If the change $p'_i - p_i$ in the frequency of A_i given in (3.3) is denoted δp_i, least-squares theory shows that

$$\sigma^2_{\mathrm{A}} = 2\overline{w} \sum_i (\delta p_i)\beta_i. \tag{4.5}$$

Since in general explicit formulae for the various β values are not available it is not possible in general to write down an explicit formula for σ^2_{A}. Fortunately this does not matter for many of the conclusions drawn below. The "genic" nature of σ^2_{A} can be seen from the following observation. In the case where only two alleles are possible at the locus, when the frequency of A_1 is at the stable equilibrium point given in (3.7) it is found that $\beta_1 = \beta_2$, so that the two alleles A_1 and A_2 are equally "fit". Further, at this equilibrium, $\sigma^2_{\mathrm{A}} = 0$. More generally, for an arbitrary number of possible alleles at the locus, evolution in the sense of allelic frequency changes occurs if and only if the additive genetic variance defined implicitly in equation (4.5) is positive. The fact that a parent passes on a gene, and not his entire genotype, to a child, and that at an equilibrium point all alleles are equally "fit", is the key to this observation.

This provides a central mathematically-derived insight into the evolutionary process. The basic Darwinian principle is that variation is necessary for evolution by natural selection: if there is no variation, no-one is more fit than anyone else and evolution by natural selection cannot occur. Thus variation is necessary for Darwinian evolution. However it is not sufficient: what is needed for evolution is *additive genetic* variation. This is a fundamental evolutionary principle. In the following sub-sections we show how the mathematical concepts of average effects and the additive genetic variance further enrich the theory of evolution.

4.2. The correlation between relatives

The analysis of biological data by mathematical and statistical methods began in earnest towards the end of the nineteenth century, and many important statistical concepts, for example correlation and regression, were developed to assist in this analysis. One matter that was extensively studied was the correlation between relatives for various metrical characters, for example height. It is clear to everyone that children to some extent resemble their parents in many such characters, and it became one of the main activities of a group of scientists, soon to become known as biometricians, to quantify and study this resemblance through the statistical concept of correlation. It was found that for almost all characters considered by the biometricians the sib/sib correlation was somewhat above the parent/offspring correlation. This raises the obvious question: "Can this and other

correlation patterns, for example uncle/nephew, be explained by Mendelian genetics?" This question can only be addressed by mathematical methods.

This question was taken up by Pearson and various co-workers soon after the rediscovery of Mendelism: see for example [7]. Pearson and Lee made the assumption, common at the time, that complete dominance was the rule at all loci controlling the characters measured (so that the effect on height of carrying two copies of the dominant allele is the same as that when carrying only one copy of the dominant allele). Their calculations led to theoretical correlation values which did not agree with the observed values, and this arose because, unknown to Pearson and Lee, dominance is not a universal phenomenon.

In the treatment above the variances $\sigma_{\rm A}^2$ and σ^2 concern the additive and the total variance in fitness. By replacing the fitness values w_{ij} by the corresponding values for any character, we can calculate the additive and the total variance for that character. In this section these variances are assumed to have this more general interpretation.

The first comprehensive treatment of this correlation between relatives problem was that of Fisher [8], who realized that the universal assumption of dominance was not appropriate for many characteristics. (This is a good place to introduce Fisher, whose work in this and other areas is often discussed below. Fisher was the leading theoretical population geneticist of the $20^{\rm th}$ century, whose work transformed the subject and who introduced many of its key concepts, including that of the additive genetic variance referred to above.)

Fisher showed, in the simple case where the character in question is determined by the genes at a single locus, mating is at random and there is no environmental component to variation, that the following formulae hold:

$$\text{correlation (parent/offspring)} = \frac{1}{2}\left\{\frac{\sigma_{\rm A}^2}{\sigma^2}\right\}, \tag{4.6}$$

$$\text{correlation (sib/sib)} = \frac{1}{2}\left\{\frac{\sigma_{\rm A}^2}{\sigma^2}\right\} + \frac{1}{4}\left\{\frac{\sigma_{\rm D}^2}{\sigma^2}\right\}, \tag{4.7}$$

$$\text{correlation (uncle/nephew)} = \frac{1}{4}\left\{\frac{\sigma_{\rm A}^2}{\sigma^2}\right\}, \tag{4.8}$$

$$\text{correlation (double first cousins)} = \frac{1}{4}\left\{\frac{\sigma_{\rm A}^2}{\sigma^2}\right\} + \frac{1}{16}\left\{\frac{\sigma_{\rm D}^2}{\sigma^2}\right\}, \tag{4.9}$$

together with various similar formulae. A comparison of equations (4.6) and (4.7) shows that these two mathematically-derived formulae agree with the empirical correlations observed by the biometricians described above.

There is an elegant simple way, devised by Malécot [9], to arrive at these and other correlations. We consider two individuals, X and Y, and define $x_{\rm f}$ as the gene that X received from his father and x_m as the gene that he received from his mother, with, for individual Y, $y_{\rm f}$ and $y_{\rm m}$ being defined similarly. We use the

symbol "≡" to denote "identical by descent", and define

$$\begin{aligned} P_{\mathrm{ff}} &= \mathrm{Prob}(x_{\mathrm{f}} \equiv y_{\mathrm{f}}), \qquad & P_{\mathrm{fm}} &= \mathrm{Prob}(x_{\mathrm{f}} \equiv y_{\mathrm{m}}), \\ P_{\mathrm{mf}} &= \mathrm{Prob}(x_{\mathrm{m}} \equiv y_{\mathrm{f}}), \qquad & P_{\mathrm{mm}} &= \mathrm{Prob}(x_{\mathrm{m}} \equiv y_{\mathrm{m}}). \end{aligned} \tag{4.10}$$

Malécot showed that when the two parents of any individual are unrelated,

$$\mathrm{correlation}(X,Y) = \frac{1}{2}\left(P_{\mathrm{ff}} + P_{\mathrm{fm}} + P_{\mathrm{mf}} + P_{\mathrm{mm}}\right)\frac{\sigma_{\mathrm{A}}^2}{\sigma^2} + \left(P_{\mathrm{ff}}P_{\mathrm{mm}} + P_{\mathrm{fm}}P_{\mathrm{mf}}\right)\frac{\sigma_{\mathrm{D}}^2}{\sigma^2}. \tag{4.11}$$

This elegant formula provides a simple method for deriving correlations for any two related individuals, and we now use it to re-derive (4.6) and (4.7).

Consider first the parent-offspring correlation, with X being the parent and Y the offspring. Since the mother and father are assumed to be unrelated, $P_{\mathrm{mm}} = P_{\mathrm{fm}} = 0$. Also $P_{\mathrm{ff}} = P_{\mathrm{mf}} = \frac{1}{2}$, and insertion of these values into (4.11) yields (4.6). If X and Y are full sibs, $P_{\mathrm{ff}} = P_{\mathrm{mm}} = \frac{1}{2}$, $P_{\mathrm{fm}} = P_{\mathrm{mf}} = 0$, and insertion of these values in (4.11) gives (4.7). Equations (4.8) and (4.9) can be found equally easily. Many other interesting conclusions can be drawn from equation (4.11). One of these is that ancestral line correlations do not contain the term involving σ_{D}^2. Thus for example the great-grandfather/great-grandson correlation is $(1/8)\sigma_{\mathrm{A}}^2/\sigma^2$, and more generally each ancestral line correlation decreases by a factor of $\frac{1}{2}$ with each additional generation separating the two individuals of interest.

In the parent-offspring correlation (4.6), the factor $\frac{1}{2}$ arises because the offspring receives only half his genes from the parent, and the factor $\sigma_{\mathrm{A}}^2/\sigma^2$ arises because the parent can only pass on an "allelic value" contribution for the character in question.

Of course essentially all measured characteristics such as height and weight are controlled by the genes at many loci, not just one locus. Also, in respect of various measurements in man (for example height) mating is not at random: tall people tend to marry tall people, and so on. Further, variation caused by the environment has to be considered. The theory has been generalized to cover these cases, but is too complex to give here. Nevertheless, observed correlations among humans for many characters followed the general pattern provided by equations (4.6)–(4.9), and thus the mathematical development provides further evidence for the importance of the Mendelian hereditary scheme.

The relevance of these calculations extends beyond evolutionary considerations. In plant and animal breeding programs the ratio $\sigma_{\mathrm{A}}^2/\sigma^2$ is called the *heritability* of a trait. It has been shown above that the additive genetic variance σ_{A}^2 has an evolutionary significance arising from the passage of genes from parent to offspring. The value of the heritability for any trait indicates, to a plant or animal breeder, the extent to which his breeding program can be expected to improve the trait of interest.

4.3. The Fundamental Theorem of Natural Selection

Ever since it was first put forward by in Fisher [10], the "Fundamental Theorem of Natural Selection" (henceforth referred to as the FTNS) has provoked as much controversy, and caused as much misunderstanding, as perhaps any other result in evolutionary population genetics. There are two aspects to the controversy surrounding the FTNS. The first is essentially mathematical: what does the theorem actually state? The second is biological: what is its biological relevance? Here we focus on the first question; for an extensive discussion of the second question see [11]. Before doing this, it is useful to make two background comments. First, Fisher saw himself as casting the main principles of Darwinian evolution in Mendelian and mathematical terms, and the FTNS, stated by him as holding the supreme position in the biological sciences, was a key component of this effort. Second, Fisher had an essentially "gene's-eye" view of evolution, and as shown below the FTNS has a gene's-eye flavor to it. This viewpoint bears on the questions of the correct level at which to describe evolution and of the appropriate unit of selection, matters which are addressed extensively in the biological literature, but which also require a mathematical treatment for their full consideration.

Fisher's various presentations of the FTNS were not consistent with each other, and the following distillation of these presentations, that "The rate of increase in mean fitness of any population at any time is equal to its additive genetic variance in fitness at that time", is generally accepted as the statement of the theorem. However, even this distilled version can be interpreted in several ways. The two main interpretations, the "classical" and the "modern", are described below. The classical interpretation is perhaps the more interesting biologically, and thus is of main interest to biologists. The modern interpretation is mathematically far deeper and is thus primarily of interest to mathematicians.

We consider first the classical interpretation. In the early years of population genetics theory various simplifying assumptions were, of necessity, made. One of these was that the individuals in a population mate at random. A second assumption often made was that, in studying the evolution of allelic frequencies at any locus through the effects of mutation and selection, all other loci in the genome can be ignored and the locus of interest treated in isolation. A third assumption, often made in connection with the second, is that the fitness of any individual depends only on the allelic types of the two genes that he carries at a single gene locus and is independent of the allelic types of the genes carried in the remainder of the genome. Some of the theory given above, and also the classical interpretation of the FTNS, reflect these simplifying (and unrealistic) assumptions. They lead to the following (classical) interpretation of the FTNS. If an arbitrary number of different allelic types is allowed at some single gene locus, if the fitness of any individual depends only on his genotype defined by these alleles, and if these genotype fitnesses are fixed constants, then assuming mating is random, the population mean fitness will increase from one generation to the next, or at least remain constant. The most straightforward proof of this classical version of the theorem,

under these assumptions, was given by Kingman [12]. Kingman further showed that when $\overline{w} = 1, \Delta\overline{w} \approx \sigma_A^2$, where $\Delta\overline{w}$ is the change in the mean fitness between parental and offspring generations and σ_A^2 is the parental generation additive genetic variance in fitness. The level of approximation involved in this statement can be seen from the fact that if single-locus genotype fitnesses differ from each other by a small term of order δ and if $\overline{w} = 1$, the value of $\Delta\overline{w}$ differs from σ_A^2 by an extremely small term (of order δ^3).

It is easy to find examples for which mean fitness decreases between parental and offspring generations if random mating is not the case. Thus the random mating requirement is essential for the classical version of the theorem. It is also a standard result of population genetics theory that population mean fitness can decrease from one generation to the next, even under random mating, if (as is the case in practice) the fitness of any individual depends on the allelic types of the genes that he carries at more than one gene locus. Thus the assumption that fitness depends on the genes at one gene locus is also essential for the classical version of the theorem. The classical interpretation of the FTNS is attractive in that it appears to quantify in Mendelian terms the two prime themes of the Darwinian theory, namely that variation is needed for evolution by natural selection and that evolution by natural selection is a process of steady improvement in the population. Also, cases where mean fitness decreases from one generation to the next are either comparatively rare, and when these decreases arise they are often small. When fitness differentials are small, the population mean fitness "usually" increases under random mating when fitness depends on the genes at many loci, and when $\overline{w} = 1$ the change in mean fitness is "usually" approximately equal to σ_A^2, thus generalizing Kingman's result given above [13, 14].

We now turn to the modern interpretation of the FTNS. The assumptions made in, and the conclusion of, the classical version of the FTNS contradict various claims that Fisher made about the theorem. First, the fact that $\Delta\overline{w}$ is not exactly equal to σ_A^2 contradicts Fisher's claim that the FTNS is an exact result and not an approximation. Second, the fact that the population mean fitness can decrease under non-random mating contradicts his claim that the FTNS is true under any form of mating. Finally, the fact that even under random mating the population mean fitness can decrease when the fitness of any individual depends on the genes that he carries at more than one locus contradicts the claim by Fisher that the FTNS holds when fitness depends on the allelic types of the genes carried by any individual at all loci in the genome. There are thus severe difficulties in reconciling the classical version of the FTNS with Fisher's explicitly stated views. The modern interpretation of the theorem resolves all these difficulties since it is an exact result, holds under non-random mating, and applies when the fitness of any individual depends on the allelic types of all the genes in his genome.

The modern interpretation of the FTNS was first proposed by Price [15]. Price claimed that Fisher was not interested in the total change of mean fitness ($\Delta\overline{w}$ above), but rather only in that part of the total change due to natural selection,

or (more or less equivalently) due to changes in allelic frequencies. Here we refer to this as the "partial change" in mean fitness. To define this change we consider first the simple case where fitness values depend on the genotype of an individual at one gene locus only. Random mating is *not* assumed.

Suppose then that the fitness of any individual depends entirely on his genotype at a single locus at which may occur alleles $A_1, A_2, \ldots, A_k$. As above we denote the frequency of the genotype A_iA_j at the time of conception of the parental generation by P_{ii} (when $i = j$) and $2P_{ij}$ (when $i \neq j$). These frequencies are not necessarily in Hardy-Weinberg form, since random mating is not assumed. The frequency p_i of the allele A_i at this time is $\sum_j P_{ij}$. The fitness of an individual of individuals of the genotype A_iA_j is w_{ij}, and the mean population fitness is $\sum_i \sum_j P_{ij} w_{ij}$. As noted above, Fisher's main evolutionary focus was on the genes in any individual at the locus of interest, not the genotypes, since it is a gene and not the genotype that is passed on from parent to child at that locus. He therefore thought of the mean population fitness as being given not by the above expression but by an expression involving the average effects of the various alleles as defined implicitly in (4.2), namely as

$$\sum_i \sum_j P_{ij}(\beta_i + \beta_j). \tag{4.12}$$

This change of viewpoint is however a purely conceptual, since the two expressions $\sum_i \sum_j P_{ij} w_{ij}$ and $\sum_i \sum_j P_{ij}(\beta_i + \beta_j)$ can be shown to be numerically identical. Despite this identity, the new conceptualization (4.12) is central to Fisher's view of the between-generation partial change in mean fitness. This was conceived as the between-generation change in the expression in (4.12) brought about by changes in the genotype frequencies P_{ij}, with the changes in the average effects β_i and β_j (which do in fact occur) being ignored. This generation-to-generation partial change in mean fitness, denoted by $\Delta_{\mathrm{P}}(\overline{w})$, (the suffix "P" denoting "partial") is, clearly,

$$\Delta_{\mathrm{P}}(\overline{w}) = \sum_i \sum_j (P'_{ij} - P_{ij})(\beta_i + \beta_j) = \sum_i \sum_j (\delta P_{ij})(\beta_i + \beta_j), \tag{4.13}$$

where P'_{ij} is the daughter generation frequency of the genotype A_iA_j, defined as for the parental generation value at its time of conception, and δP_{ij} is the between generation change in the ordered frequency of this genotype. The extreme right-hand term in (4.13) is easily shown to be $2\sum_i (\delta p_i)\beta_i$, and equation (4.5) then shows that the partial change in mean fitness is exactly $\sigma^2_{\mathrm{A}}/\overline{w}$, whether or not random mating occurs. This result, involving no approximations, is the modern interpretation of the single-locus FTNS.

The parallel whole-genome statement of the theorem, applying when the fitness of any individual depends in an arbitrary way on all the genes in the genome, can be found as follows. Assume that the various (gigantically large number of) possible whole-genome genotypes are listed in some agreed order as genotypes $1, 2, \ldots, s, \ldots, S$. The "time of conception" frequency of the typical genotype s in

the parental generation is denoted by g_s and the fitness of this genotype by w_s. Thus the parental generation population mean fitness, denoted (for the whole-genome as for the one-locus case) by $\sum_s g_s w_s$.

As in the one locus case, the average effects of the various alleles at the various loci in the genome are defined by a least-squares procedure. These average effects of all the alleles in the genome are determined by minimizing the sum of squares

$$\sum_g g_s \left\{ w_s - \sum c_i^{\mathrm{A}} \beta_i^{\mathrm{A}} \right\}^2 . \tag{4.14}$$

In the expression (4.14), β_i^{A} is the average effect of A_i at the typical gene locus A, the outer sum is taken over all whole-genome genotypes and the inner sum is taken, for each whole-genome genotype, over all alleles at all loci in the genome contained within that genotype, with $c_i^{\mathrm{A}} = 1, 2$ or 0 depending on whether A_i arises once, twice or not at all within the genotype g_s, at the locus A.

It is not necessary to give explicit formulae for the various β values defined by this least-squares procedure: indeed they can only be expressed implicitly as the (unique) solution of a gigantic set of simultaneous equations. As in the one-locus case, the Fisher's "gene's-eye" view of the fitness of the typical whole-genome genotype s is not its actual fitness, but instead is the linear combination $\sum c_{ai}\beta_{ai}$, defined as above. In parallel with the one-locus case analysis, the mean fitness of the population is now thought of as being

$$\sum_g g_s \left\{ \sum c_i^{\mathrm{A}} \beta_i^{\mathrm{A}} \right\}, \tag{4.15}$$

which (as in the corresponding one-locus case) is numerically identical to that given by the standard definition of mean fitness, here $\sum_s g_s w_s$ given above.

Again in parallel with the one-locus case, the partial change $\Delta_{\mathrm{P}}\overline{w}$ in mean fitness is defined as the change in the expression (23) derived solely from the changes Δg_s in the various whole-genome genotype frequencies and ignoring the changes in the β values, namely

$$\sum_g \Delta g_s \left\{ \sum c_i^{\mathrm{A}} \beta_i^{\mathrm{A}} \right\}. \tag{4.16}$$

The resulting expression can be shown to be equal to $\sigma_{\mathrm{A}}^2/\overline{w}$, where σ_{A}^2 now denotes the whole-genome additive genetic variance, defined in a manner extending that for the one-locus case. This simple and exact result is the modern interpretation of the whole-genome FTNS [16, 17]. It is true whatever the mating scheme. It is inconceivable that this "gene's-eye" view of evolution could have been obtained by anything other than a mathematical treatment. Further, the mathematical treatment provides an insight into evolutionary principles not obtainable in any other way.