Mathematics of Evolution

Fred Hoyle

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In Memory of George Carson

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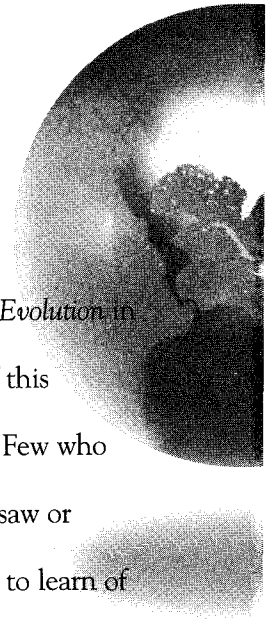
Foreword



After Fred Hoyle wrote *Mathematics of Evolution* in 1987, only a hundred facsimile copies of this handwritten manuscript were produced. Few who would be interested in its contents ever saw or heard about the manuscript. I happened to learn of it from Hoyle's longtime collaborator, Chandra Wickramasinghe, who gave me a copy when I visited him in Cardiff, Wales, in 1995. I was deeply impressed with the penetrating analysis it contained and moved by the story behind its dedication to George Carson.

The following year I met Sir Fred Hoyle at the Institute for Astronomy in Cambridge, England, which Hoyle had founded in 1967 and headed for six years. There, in the former residence of Sir Arthur Eddington, he spoke with me at length about his work in biology. I came away with even greater admiration for his integrity and his contributions to science and with genuine affection for him. It seemed a tragedy that his *Mathematics of Evolution* had not been typeset and widely distributed. Concerned that this work might be lost to a larger audience, I asked him if I could publish it, and he agreed. In 1997, he wrote a new preface and oversaw the minor revisions required.

Other scientists, such as J. B. S. Haldane, R. A. Fisher, Sewall Wright and Motoo Kimura, have worked extensively on this subject, and Hoyle is equal to any of them in mathematical skill. Being iconoclastic, he is not discouraged when his analysis leads to a result different from that reached by his predecessors. And Professor Hoyle tells a story well. Even the complex mathematics in some chapters are narrated with straightforward, simple and engaging text. This is a book that many readers —not just those who are mathematically sophisticated—can easily benefit from and enjoy. But there is even more here of value for geneticists, mathematicians, and scientists in any field who are interested in evolution. In fact, the greatest purpose this book could serve would be to rekindle within mainstream science broad, fair and serious consideration of the issues it raises.

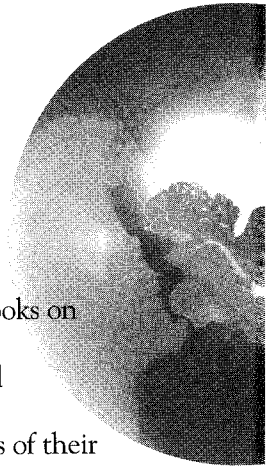
This is the first book I have published and it took more time and effort than I expected. But here it is. Finally. I am grateful to Meg Johnson, who mastered Hoyle's handwriting and keyed the text and equations into the computer accurately, and in record time. I am extremely grateful to Diane Nesin, who also mastered Dr. Hoyle's handwriting, edited the typescript, communicated with Sir Fred, transcribed his revisions, resolved vexing software conflicts, helped me find other resources, and encouraged me to stick with it. I am grateful to Robbin Brent, who made the design and production of the book a smooth and enjoyable process. I always appreciate the superb and steady assistance of my administrator, Barbara Mason,

without whom I would be incapacitated. And my deepest thanks to my wife, Ellen, who provided loving and essential support, instead of recommending psychological counseling, after I left a perfectly good job to pursue science full time.

Finally, I am grateful to Sir Fred Hoyle for doing science so tirelessly and courageously.

—Brig Klyce
25 May 1999

Preface



There is a fair flow of anti-Darwinian books on the market. Although some contain valid arguments against the theory, the motives of their authors seem to me to be rarely scientific. The motive is rather to cast doubt on the concept of evolution, in order to encourage a return to religious fundamentalism, causing biologists to toss such books on sight into the wastepaper basket. Causing them perhaps to wonder if it

might not be the same with this book. Well, it isn't. Admittedly, I was brought up in the British state school system *circa* 1925, which was certainly religiously oriented to an extent Americans will hardly credit. In fact, I scored well in religious examinations on account of an early faculty for being able to commit long passages from the Bible to memory. Add to this that I was one of the members of our local church choir.

Our church wasn't sufficiently grand to have its own vicar. But the diocese assigned us a curate who would on most Sundays climb the hill from the nearest town to our village. For variety's sake if not for his own, he would get other curates to stand in for him every two or three weeks, and sometimes a lay preacher. We boys liked the lay preachers, because once they got fairly started, they would mostly foam along with little regard for vocabulary or syntax. One day, a small thickset man in boots clumped up the wooden steps to the pulpit. After a minute or so taken in settling himself, he suddenly roared out to our innocent-looking congregation: "The number of the beast: for it is the number of a man: and his number is six hundred three score and six."

It didn't take long for me to work out that six hundred three score and six was 666, numbers being something with which I regarded myself as being fairly expert. Did this mean the number of men in the world was claimed to be 666? Or did it mean what it said literally—that 666 was a number attached to a particular man in the fashion of a convict? Either way I felt little doubt that this particular preacher was seriously daft in the head. When I asked our teacher of religion at school about it, I was told that the text was from the Book of Revelations, which perhaps shouldn't be taken too seriously. Maybe not, but for me it was a wave of a incoming tide licking away at a sand castle.

The sand castle was entirely washed away all in a moment about two years later. This time there would be no doubt about the source or the topic. The sources were the sacred gospels of Matthew, Mark, Luke, and John; and the topic was central to Christian faith, the Resurrection. I had the thought one day to look up and compare what the four gospels had to say about events of at the tomb of Christ, explicitly with reference to these questions: Who among Christ's friends, relatives, and disciples first came to the tomb? What was the physical condition of the tomb? and How many angels were present there? To this point I had been willing to accept such supernatural agents as angels. Indeed, angels seemed to me so remarkable that it mattered quite a lot whether there was one of them, two of them, or three of them in

attendance. What I found was that no two among Matthew, Mark, Luke, and John agreed in respect of this simple question of angel numeration, which even the most slow-witted person in my native village would have been able to report correctly.

Like a boat pushed off into a fast-moving river, I was swept away from my former cherished beliefs. Out of my local church in a week. Out of my belief in the Christian religion in not much time. out of any belief in any fundamental religion in little more time than that. Since then, the boat has continued on its journey, away from any belief in anything which men have written down on paper a long time ago.

The criticism of the Darwinian theory given in this book arises straightforwardly from my belief that the theory *is* wrong, and that continued adherence to it is an impediment to discovering the correct evolutionary theory. To the extent that one is deflected by socioreligious considerations from correcting what is wrong, one hands a victory to opponents.

To deny the paleontological evidence of evolution, and in particular man's place in it, is on par with denying that water flows downhill. In the Darwinian theory, while water flows downhill all right, it flows in rivers that are claimed to be uniformly graded, a graded river being one that goes downhill at a steady angle from its source to the sea. Because rivers in practice flow over rocks of uneven hardness, they sometimes hurry downhill and they sometimes dawdle.

The River Wharfe in its flow over limestone rocks above the village of Burkden goes in a series of small falls over ledges a foot or two in height, intervals of little change spaced by small jumps. The name "punctuated equilibrium" has been given to evolution proceeding analogously to this. But water can also go downhill far more spectacularly, as with the Niagara River between Lake Erie and Lake Ontario. It is to biological events on such a scale that in later sections of this book I have given the name "genetic storm."

The biggest physical storm occurring in ten years usually produces as much change as all the rest put together. And the biggest in a hundred years as much or more than all the rest. And, perhaps, even the biggest in a thousand years. ... Something of the same sort seems to happen with evolution. The fine-tuning of genes produces small changes. The addition of entirely new genes, perhaps whole batteries of new genes, produces large changes, grafted onto the genetic complement of an already-existing organism.

A decade ago I thought new genes were acquired by an organism from the external environment, just as bacterium acquires a new gene by picking up a plasmid, except that, unlike the bacterial case, its external environment was taken to be external to the Earth. At acquisition, a new gene was supposed to go first into the store of redundant DNA, a process continuing until a considerable number had been added, when, in a genetic storm, cell programs become shuffled by a viral form of interference from outside. Most such shufflings would come to a bad end. Buy occasionally a situation both new and workable in a new niche in the terrestrial environment was considered to arise, setting evolution off on a new path.

Today, however, I would modify this picture somewhat to the view that all genes in present-day organisms were here already in the metazoans that invade the Earth 570 million years ago at the beginning of the Cambrian Era, making the subsequent story of terrestrial evolution into one in which genes have been called into operation as ecologic conditions permitted them to be so. For example, it would have been pointless call in a genetic system leading to the appearance of flowering plants before the means of successful pollination existed. The intricate interweaving of many organisms had to proceed in concert with each in a pattern that has grown every more complex with the passage of time. The first metazoans were relatively simple forms that could exist by themselves on an undeveloped Earth, but they already possessed the genes necessary for their subsequent development.

This is a more efficient way of seeding a planet with life than a genetically random process of acquiring genes would be. If life exists in the universe on a very grand scale, we would be likely to have received it on the run only after a great deal of evolution had already taken place. In which case, the most efficient procedures would have become established already by 570 million years ago.

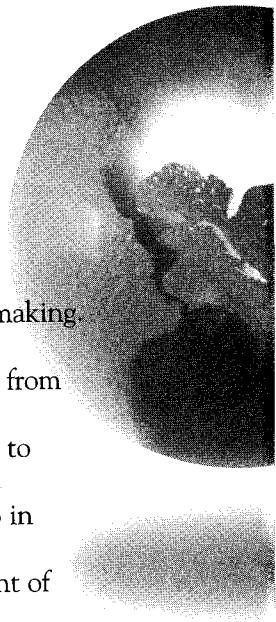
Genes that are initially unexpressed accumulate errors by neutral drift at a rate of ~10^{-6} errors per gene per generation. After a geological interval of ~10^{8} years, which implies 10^{8} generations, there would thus be ~100 errors among ~1000 base pairs for each gene that was being held in storage against future evolution, resulting in a serious loss of efficiency by the time such store genes come to be activated. But providing mating of population number N of the first organisms were large enough, efficiency would quickly be recovered. By the arguments of Chapter 4, the probability of ever becoming fixed by random drift would be $1/2N$. Hence so long as N is large compared

with the number of generations over which drift occurs, no irrevocable damage occurs.Whereas about a tenth of the population would have a particular base pair wrong on the DNA of a gene unprotected by natural selection, ~100 million years, nine-tenths of the population would still have it right. Then, once the gene is activated, replication in sexual cycles with crossover removes the errors quickly by natural selection, in a length of time that is geologically negligible.

It is a deduction that the first organisms 570 million years ago would have needed genetic protection by crossover, as described in Chapter 2; and reproduction by pathogenesis would probably also be necessary in order to ensure that N becomes large enough for the two sexes to find each other successfully. Judging as best one can from living fossils dated beyond 500 million years ago, these requirements seem to be well met.

—Fred Hoyle
Bournemouth

Introduction



This essay has been a long time in the making. My earliest research work was in truancy from school, in which I was successful enough to whittle down the time I spent mewed up in classrooms to something like forty percent of what it was supposed to be between the ages of five and nine. It was an essential part of my system that neither the school nor my parents should know where I was during the daytime.

I simply disappeared, like H. G. Wells's Invisible Man, except that being only a small boy, it was easier for me. I disappeared into the woods and fields, with plenty of time to watch birds building their nests, to watch the rain falling and the streams rising. So it came about that I knew the names of every flower and tree and the whereabouts of every animal in my home district.

All that homespun knowledge was wiped clean from my brain by the age of eighteen, because by then I had become convinced that biology was a doubtful subject. The trouble was that in reading widely during my early teens I ran into the Darwinian theory, for a little while with illusions and then with less respect than adults with bated breath were wont to show. The theory seemed to me to run like this:

> If among the varieties of a species there is one that survives better in the environment than the others, then the variety that survives best is the one that best survives.

If I had known the word tautology I would have called this a tautology. People with still more bated breath, called it natural selection. I made them angry, just as I do today, by saying that it did nothing at all. You could select potatoes as much as you pleased but you would never make them into a rabbit. Nor by selecting oak trees could you make them into colonies of bats, and those who thought they could in my opinion were bats in the belfry. This made them angry too. Older folk in the know told me that selection didn't operate to make complicated things out of complicated things, only to make complex things out of simple ones. I couldn't understand how anything of the sort could be true, because, unlikely as it was, it would surely be less difficult to make a rabbit out of a potato than to make a rabbit out of sludge, which is what people said had happened, people with line after line of letters after their names who should have known what they were talking about, but obviously didn't.

The Mathematical Tripos at Cambridge intervened to occupy my thoughts, and it was not until I began research officially in 1936 that biology reared its head again. This was because I became friendly with George Carson who was then just completing his Ph.D. in botany. In 1938–39 I shared "digs" with George, so biological topics naturally occupied a fair fraction of our conversation. Carson was among a minority of biologists who have suspected something to be amiss with the Darwinian theory. His position was similar to

that of Alfred Russel Wallace in the latter's later years. Something was right about the theory(there were too many examples of niche matching between special characteristics of species and the precise details of their environment for the theory not to be correct in some degree(but not wholly correct. George was pretty well unique in believing that what was missing could be discovered by mathematics. He never ceased, both in our student days and in later life, trying to inveigle me into a serious investigation of evolution, and when I did not rise to the bait, George was forever borrowing my mathematics books. He would sit with them of an evening with the conviction that somewhere he would find the clue he was looking for. Neither of us spotted this clue, namely that terrestrial biology is not a closed system.

It was—and still is—very hard to arrive at this concept from inside biology. The trouble lay in an unremitting cultural struggle which had developed from 1860 onward between biologists on the one hand and the supporters of old beliefs on the other. The old believers said that rabbits had been created by God using methods too wonderful for us to comprehend. The new believers said that rabbits had been created from sludge, by methods too complex for us to calculate and by methods likely enough involving improbable happenings. Improbable happenings replaced miracles and sludge replaced God, with believers both old and new seeking to cover up their ignorance in clouds of words, but different words. It was over the words that passions raged, passions which continue to rumble on in the modern world, passions that one can read about with hilarious satisfaction in the columns of the weekly science magazine *Nature* and listen to in basso profundo pronouncements from learned scientific societies. Because the old believers said that God came out of the sky, thereby connecting the Earth with events outside it, the new believers were obliged to say the opposite and to do so, as always, with intense conviction. Although the new believers had not a particle of evidence to support their statements on the matter, they asserted that the rabbit-producing sludge (called soup to make it sound more palatable) was terrestrially located and that all chemical and biochemical transmogrifications of the sludge were terrestrially inspired. Because there was not a particle of evidence to support this view, new believers had to swallow it as an article of faith, otherwise they could not pass their examinations or secure a job or avoid the ridicule of their colleagues. So it came about from 1860 onward that new believers became in a sense mentally ill, or, more precisely, either you became mentally ill or you quitted the

subject of biology, as I had done in my early teens. The trouble for young biologists was that, with everyone around them ill, it became impossible for them to think they were well unless they were ill, which again is a situation you can read all about in the columns of *Nature*.

I eventually returned willy-nilly to biology in the following way. My colleague Chandra Wickramasinghe and I had for a long time been trying to explain the observed properties of interstellar grains. The sheer quantity of the grains tells one that they must be made out of common atoms, so at first sight it seems as if they could only be made from commonplace materials. However, the more we compared the astronomical observations with the properties of commonplace materials, the more we found that nothing fitted as accurately as it should have done. The basic trouble was that all solid ordinary materials have refractive indices that are much too high, a difficulty that could only be got over if the interstellar particles were hollow. But why the particles should be hollow remained a mystery until some years ago we happened to notice that bacteria become hollow when they dry out—and bacteria if they existed in interstellar space would certainly be very dry. After so many failures we had by now arrived at a try-anything attitude. Equipping ourselves with a size distribution for bacteria taken from standard catalogues, we were able to make a comparison with the astronomical data, finding essentially precise agreement, agreement far superior to anything we had obtained from commonplace materials.

This success was for visual wavelengths. The next question was, What is the situation at other wavelengths? To this end, we were led, together with Dr. Shirwan Al-Mufti, to investigate the properties of microorganisms at longer wavelengths in the infrared. From measurements made in the laboratory by Al-Mufti, we found a remarkable constancy of the absorption pattern at wavelengths near 3.4μm, constancy from one microorganism to another, and constancy also with respect to the physical conditions. Not long after our measurements had been made, the absorption properties of interstellar grains were actually determined observationally, with an uncannily close correspondence found to those of microorganisms. Since this second success was predictive, we were encouraged to follow up the concept of life existing outside the Earth, with especial reference to simple organisms and to the genetic components of life. The taboo which had hitherto existed for such thinking, at any rate for us, was broken.

We were thus led to considerations in a number of directions which have been fully reported elsewhere, including the evolutionary considerations touched on here in Chapter 6. As it became clear that the Darwinian theory could not be broadly correct, a question still remained, however, for I found it difficult to accept that the theory could be wholly incorrect. When ideas are based on observations, as the Darwinian theory certainly is, it is usual for those ideas to be valid at least within the range of the observations. It is when extrapolations are made outside the range of observations that troubles may arise. So the issue that presented itself was to determine just how far the theory was valid and exactly why beyond a certain point it became invalid. The issue was a mathematical one, as George Carson had suspected so long ago, and I thought at first that it might be settled the easy way, by reading in the literature and in classic texts on mathematical genetics.

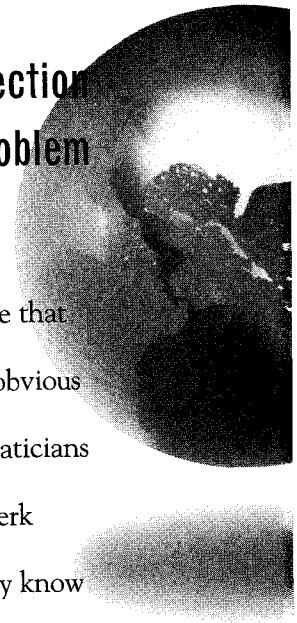
My experience proved unrewarding. After a session with "the books," I would retreat, baffled. The mathematics was never difficult in itself. It was the words in which the mathematics was shrouded—one example concerning so-called genetic cost is given in Chapter 7. At first I took the fault to be mine, but as the frustrating sessions were repeated again and again over a period of years, I came to suspect that the confusion was in the heads of the writers themselves. Eventually therefore, I decided to tackle this mathematics myself working *de novo*, and so coming at last to the problem George Carson had tried to set me half a century ago. Although my results were all arrived at independently, some—perhaps most—have been obtained before. Their arrangement, however, is I believe original.

Of the books, I would like to recommend especially R. A. Fisher's *A Genetical Theory of Natural Selection* for its brilliant obscurity. After two or three months of investigation it will be found possible to understand some of Fisher's sentences. I am genuinely sorry for scientists of the younger generation who never knew Fisher personally. So long as you avoided a handful of subjects like inverse probability that would turn Fisher in the briefest possible moment from extreme urbanity into a boiling cauldron of wrath, you got by with little worse than a thick head from the port which he, like the Cambridge mathematician J. E. Littlewood, loved to drink in the evening. And on the credit side you gained a cherished memory of English spoken in a Shakespearean style and delivered in the manner of a Spanish grandee.

And the outcome of this essay? Well as common sense would suggest, the Darwinian theory is correct in the small but not in the large. Rabbits come from other slightly different rabbits, not from either soup or potatoes. Where they came from in the first place is a problem yet to be solved, like much else of a cosmic scale.

Chapter 1

Natural Selection and the Multigene Problem



Commonly I find physicists who tell me that natural selection seems to them but an obvious application of simple feedback. Mathematicians on the other hand tend to give a knee-jerk shudder at the word *obvious* because they know of so many cases where what at first sight seemed "obviously" true turns out on careful investigation to be untrue. Natural selection turns out to be untrue in the general sense in

which it is usually considered to apply, as I shall demonstrate in this chapter. But in the more restrictive sense introduced in the next chapter the theory does better; with what degree of success, I will consider in Chapter 6.

Let us start naively with the feedback equation

$$\frac{dx}{dt} = sx \quad , \tag{1.1}$$

in which x is considered to be the fraction of some large population that possesses a particular property, A say, the remaining fraction $1 - x$ possessing a different property a, all individuals being otherwise similar to each other. The population reproduces itself from generation to generation with the old dying to make way for the young. Change occurs so slowly that time can be regarded as a continuous variable with the average interval between generations taken as unit. Individuals with properties A and a in a particular generation are considered to produce offspring in the ratio $1 + s : 1$, offspring that survive to become reproductive agents in the next generation, with s taken as a constant independent of x and t.

Equation (1.1) integrates to give

$$x = x_0 \exp(st) \quad , \tag{1.2}$$

where $x = x_0$ at $t = 0$ is a given boundary condition. So it is agreed for $s > 0$, with A then a favourable property, that x rises to unity with all members of the population coming to possess it in a time span of $-1n\ x_0/s$ generations. For example if $x_0 = 10^{-6}$ and $s = 0.01$, the time span would be about 1400 generations, small compared to the intervals involved in biological evolution. And if $s < 0$ the solution dies away in a time span of order $1/s$ generations, thereby implying that if A is unfavourable it will be quickly rejected.

I am convinced it is this almost trivial simplicity that explains why the Darwinian theory is so widely accepted, why it has penetrated through the educational system so completely. As one student text puts it, "The theory is a two-step process. First variation must exist in a population. Second, the fittest members of the population have a selective advantage and are more likely to transmit their genes to the next generation."

But what if individuals with a good gene A carry a bad gene B having the larger value of $|s|$. Does the bad gene not carry the good one down to disaster? What of the situation that bad mutations must enormously exceed good ones in number? Let us take a first look at the comparative rates at which good and bad mutations are likely to arise. Most mutations consist of a base pair being changed during the copying of DNA. Because amino acids are coded for by triplets of base pairs with 64 different triplets available for only 20 amino acids, the genetic code has an approximately 3 to 1 redundancy in it. This can be taken care of to sufficient accuracy here by letting the third member of each triplet be considered redundant. If we set $3 \cdot 10^{-9}$ as the chance of any particular base pair being miscopied, the chance of any amino acid being changed in the protein to which a gene gives expression is $\sim 6 \cdot 10^{-9}$. Thus a protein with about 160 amino acids in its chain would have a chance of 1 part in a million of being miscopied—that is, if of one amino acid in its chain being changed in a random way.

A single set of mammalian chromosomes has approximately $3 \cdot 10^9$ base pairs, of which perhaps 95 percent play no active role, most of the DNA being apparently nonfunctional with respect to gene products. Taking $\sim 10^8$ base pairs as the total number which are genetically relevant, the mutation rate λ per single chromosome set is $\sim 3 \cdot 10^{-9} \cdot 10^8 \cong 0.3$ per generation. For two chromosome sets the rate is ~ 0.6 per generation, so that a considerable fraction of individuals born in every generation exhibit some new mutation, the great majority being harmful in some degree. The essential problem for the Darwinian theory in its twentieth-century form is how to cope with this continuing flood of adverse mutations, a far cry indeed from the trite problem of only the single mutation in (1.1). Supposing a favourable mutation to occur among the avalanche of unfavourable ones, how is the favourable mutation to advance against the downward pressure of the others?

Merely seeking to remove bad mutations by inverse mutations which return genes back to their original forms is a useless enterprise. Suppose that compared to an original pristine genetic structure a species has been penetrated by a hundred deleterious mutations each with $s = -0.01$, so that the loss of competitive fitness compared to the original situation is $(1 - 0.01)^{100} \cong e^{-1}$. For a single adverse mutation the chance of being set right by an inverse mutation $\sim 10^{-9}$ per generation. Hence the correction rate for 100 adverse mutations is $\sim 100 \cdot 10^{-9} = 10^{-7}$ per chromosome set per

generation. Compared to the ongoing rate of ~0.3 adverse mutations per chromosome set per generation the correction rate is extremely small. If the flood of deleterious mutations is to be held in check, natural selection must therefore do the job, not inverse mutations.

The reason why most mutations must be bad is of course that random changes made to any complex structure lead to many more downward steps in the operating efficiency of the structure than to upward steps. How the occasional lucky improvement is to lead to positive evolution is a puzzle that has disturbed many mathematicians. In a budding model or a binary fission model, in both of which progeny inherit the genetic structure of a single parent, the situation appears unpromising. Rare favourable mutations in such models cannot free themselves from the more frequent unfavourable ones, because an offspring to whom a rare favourable mutation occurs is inevitably saddled with all the unfavourable mutations which have afflicted its parental line.

To have any hope of success the neo-Darwinian theory must therefore appeal to a reproductive model quite different from the model mostly adopted by single-celled organisms. This is already an immense climb down from what is usually claimed for the theory. Gone is its "obvious" status. Only if a model can be found that contrives to uncouple the selective properties of one gene from another, permitting the occasional good mutation to survive and prosper in a sea of bad mutations, can evolution be made to work at all. How exquisitely complex the model needs to be to achieve such a remarkable result will be discussed in the next chapter. Then the mathematical properties of the complex model will be investigated up to the end of Chapter 5. Thereafter, in Chapter 6, we shall be in a position to discuss the extent to which the neo-Darwinian theory can be considered to work and the extent to which it cannot. To anticipate the eventual outcome it will be found that, subject to the choice of a highly sophisticated reproductive model, the theory works at the level of varieties and species, just as it was found empirically to do by biologists from the mid-nineteenth century onward. But the theory does not work at broader taxonomic levels; it cannot explain the major steps in evolution. For them, something not considered in the Darwinian theory is essential.

To begin the present consideration of a single parent-to-offspring model, let us note that equation (1.1) was not normalized properly to maintain a stable population from generation to generation. Suppose the average

number of offspring surviving to reproductive age from an individual possessing gene type A is $\alpha\,(1+s)$, compared to α for the offspring from an average individual of gene type a. Then for a stable population to be maintained $\alpha\,(x)$ must be a function of the fraction x of the population with A that is given by

$$\alpha\,\left[(1+s)x+1-x\right] = 1 \quad . \tag{1.3}$$

Taking the generation interval as the unit of the time t, a differential equation for $x(t)$ can be obtained from

$$x\,(t+1) = \alpha\,(1+s)x(t) \quad . \tag{1.4}$$

Writing $x\,(t+1) = x(t) + dx/dt$ and using (1.3), we have for $s << 1$

$$\frac{dx}{dt} = \frac{s\,x(1-x)}{1+s\,x} \cong s\,x(1-x) \quad , \tag{1.5}$$

which is already more complicated than (1.1). For the boundary condition $x = x_0 << 1$ at $t = t_0$, the solution of (1.5) to the first order in s is given by

$$x = \frac{x_0\,\exp(st)}{1+x_0\left[\exp(st)-1\right]} \cong \frac{x_0}{x_0+\,\exp(-st)} \quad . \tag{1.6}$$

Unlike the solution of (1.1) for $s > 0$, x does not increase to unity as $t = -\ell n\, x_0 / s$ but only to $\frac{1}{2}$. Indeed, according to (1.6) for $s > 0$, x does not increase strictly to unity at any finite time. Property A does not completely "fix" itself in the species in any finite number of generations. A residuum of individuals remain with the disadvantageous property a. This is on the supposition that each individual produces the average quota of surviving offspring for the class to which it belongs: $\alpha(1+s)$ offspring if the gene type is A, α if the type is a. In practice, however, the number of surviving offspring produced by any individual has an element of chance in it that is quite apart from the genetic situation. Because it is impossible to recover from extinction, chance operates as a one-way street. On occasion, individuals of

the worse genetic type a may be helped by luck, but such temporary good fortune is of no permanent advantage because an increase in the number of individuals of type a only gives natural selection more scope to operate. When, however, bad luck goes against individuals of type a, finally causing their number to drop to zero, a is extinct and the game is over. This combination of genetic pressure with chance environmental fluctuations is typical of many situations in biology. Whenever genetic pressure forces down the number of individuals possessing a particular property below a certain level, it is then an adverse environmental fluctuation that delivers the final blow to survival.

According to the above discussion of mutation rates, the number of potential bad mutations is of order 10^8, the number of sensitive base pairs. Write n for this number, and for simplicity take all deleterious mutations to have the same adverse selection factor $s < 0$. Also take the probability of each bad mutation appearing to be the same, λ / n, where $\lambda \cong 0.3$ is the total probability per generation of one of the mutations appearing—that is, λ is the average number of bad new mutations appearing as each offspring is born. Fluctuations given by the Poisson distribution will evidently occur from offspring to offspring, with $\lambda^k \exp -\lambda / k!$ the probability that an offspring is born with k defects. However, for λ appreciably less than unity, the Poisson distribution is dominated by $k = 0$ and $k = 1$, with probabilities $1 - \lambda$ and λ, respectively, to the first order in λ. Only these two possibilities are considered in the following equations.

Write $y_r(t)$, $r = 0, 1, 2, \ldots$, for the fractions of the population with no defect, with one defect, two defects, . . . , and write $\alpha (1-|s|)^r$ for the number of surviving offspring produced by an individual with r defects. This is in a model where from generation to generation parents die and are replaced by their offspring, the "surviving offspring" being those who themselves become parents in the succeeding generation. From the definition of the fractions y_r,

$$\sum_{r=0,1,2\ldots} y_r = 1 \quad , \tag{1.7}$$

and from the condition that the population remains stable from generation to generation, then

$$\alpha \sum_{r=0,1,2\ldots} (1-|s|)^r y_r = 1 \quad . \tag{1.8}$$

The following equations relate to fractions y_r from generation to generation with fractions in the $t + 1$ generation on the left and fraction in the t generation on the right.

$$y_0(t+1) = \{\alpha (1-\lambda) y_0\}_t \quad , \tag{1.9}$$

$$y_1(t+1) = \{ \alpha (1-|s|)(1-\lambda) y_1 + \lambda\, y_0\}_t \quad , \tag{1.10}$$

$$y_r(t+1) = \left\{ \alpha \left[(1-|s|)^r (1-\lambda) y_r + (1-|s|)^{r-1} \lambda\ y_{r-1}\right] \right\}_t \quad . \tag{1.11}$$

Taking the fractions y_r to vary slowly from generation to generation,

$$y_r(t+1) = y_r(t) + \frac{dy_r}{dt}(t) \quad , \qquad r = 0,\ 1,\ 2, \cdots \tag{1.12}$$

Hence the differential equations for $y_r(t)$ are

$$\frac{dy_0}{dt} = \left[\alpha (1-\lambda) - 1\right] y_0 \quad , \tag{1.13}$$

$$\frac{dy_1}{dt} = \alpha \lambda\, y_0 + \left[\alpha (1-\lambda)(1-|s|) - 1\right] y_1 \quad , \tag{1.14}$$

$$\cdots$$

$$\frac{dy_r}{dt} = \alpha \lambda (1-|s|)^{r-1} y_{r-1} + \left[\alpha (1-\lambda)(1-|s|)^r - 1\right] y_r \tag{1.15}$$

which are to be solved subject to the boundary conditions

$$y_0 = 1 \; ; y_r = 0 \; ; r = 1, 2, \ldots \quad \text{at time } t = 0 \quad . \qquad (1.16)$$

Remembering that the normalization factor α is a function of time according to (1.8), we evidently have a set of nonlinear equations for determining the flow of the deleterious mutations, a set that is finite, although y_r may become nonzero at moderate or high values of r.

Initially $\alpha = 1$, so that the coefficient of y_0 on the right-hand side of (1.13) is $-\lambda$ at first. Hence y_0 declines initially as $\exp -\lambda t$, which for $\lambda = 0.3$ is a steep fall needing only a few generations for the effect to show in a considerable fall away of y_0. Equation (1.14) gives an initial buildup of y_1 that is often encountered in flow problems of this kind. Because of the $\alpha\lambda y_0$ term on the right-hand side of (1.14), y_1 at first increases but is then checked by the $-[\alpha(1 - \lambda)(1 - |s|) - 1]\, y_1$ term. Thus y_1 rises at first, then y_1 attains a maximum as the two terms on the right-hand side of (1.14) cancel each other, and thereafter y_1 falls away to a lower value. As time goes on $y_2, y_3, \ldots$, show a similar behavior. A time plot for y_0 would show a curve that declines steeply at first and then levels out to some ultimate value, $\bar{y}_0$ say, while time plots for $y_1, y_2, \ldots$ are curves that rise initially from zero to maxima and then fall away and level out at ultimate values, $\bar{y}_1, \bar{y}_2, \ldots$ say. Our problem is to calculate these ultimate values, attained in time scales $\sim 1/|s|$ generations.

As the ultimate values $\bar{y}_0, \bar{y}_1, \ldots$ are attained, the right-hand sides of equations (1.13) to (1.15) go to zero. The inverse procedure of setting the right-hand sides of (1.13) to (1.15) to zero is not sufficient, however, to determine $\bar{y}_0, \bar{y}_1, \ldots$. This is because such a procedure does not lead to a unique result. The problem that remains therefore is to determine which among a number of possibilities for $\bar{y}_0, \bar{y}_1, \ldots$, is the solution belonging to the boundary conditions stated in (1.16). Each solution for $\bar{y}_0, \bar{y}_1, \ldots$, is characterized by an integer, q say, such that a coefficient in one of the equations becomes zero,

$$\bar{\alpha}\,(1-\lambda)(1-|s|)^q - 1 = 0 \quad , \quad q = 0, 1, 2, \ldots \quad , \qquad (1.17)$$

where $\bar{\alpha}$ is given by

$$\bar{\alpha} \sum_{r=0,\,1,\ldots} (1-|s|)^r \bar{y}_r = 1 \quad . \qquad (1.18)$$

The solution for $\bar{y}_0, \bar{y}_1, \ldots$, is then

$$\bar{y}_r = 0 \quad , \text{ if } r < q \quad , \qquad (1.19)$$

while for $r \geq q$ the recurrence relation

$$\bar{\alpha}\,\lambda\,(1-|s|)^r \bar{y}_r = -\left[\bar{\alpha}\,(1-\lambda)\,(1-|s|)^{r+1} - 1\right]\bar{y}_{r+1} \qquad (1.20)$$

together with

$$\sum_{r=q,\,q+1,\ldots} \bar{y}_r = 1 \qquad (1.21)$$

completes the solution. Let us carry this procedure through explicitly for the case $q = 0$, when none of the $\bar{y}$ values is zero.

In the case $q = 0$, equation (1.17) gives

$$\bar{\alpha}\,(1-\lambda) = 1 \quad , \qquad (1.22)$$

and equation (1.20) takes the form

$$\bar{y}_r = \frac{\lambda}{1-\lambda}\,\frac{(1-|s|)^{r-1}}{1-(1-|s|)^r}\,\bar{y}_{r-1} \quad , \qquad (1.23)$$

which for $|s| << 1$ can be written to sufficient approximation as

$$\bar{y}_r = \frac{\lambda}{1-\lambda} \frac{1}{\exp(r|s|)-1} \bar{y}_{r-1} \quad . \tag{1.24}$$

Assuming for the moment that this case $q = 0$ belongs to the specified boundary conditions (1.16), we could say the appearance of the exp $(r|s|)$ factor in (1.24) is something of a triumph for natural selection, for it cuts off the $\bar{y}_r$ values sharply for $r \geq \sim 1/|s|$. A similar treatment for $q \neq 0$ modifies (1.24) to

$$\bar{y}_r = \frac{\lambda}{1-\lambda} \frac{1}{\exp[(r-q)|s|]-1} \bar{y}_{r-1} \quad , \tag{1.25}$$

giving a similar cutoff, but with a distribution for population members having q more defects than in the case $q = 0$. From this observation we can see already that the case $q = 0$ is going to be the best one from a biological point of view, permitting the least penetration of defects into the population.

Continuing explicitly for $q = 0$, we have

$$\bar{y}_1 = \frac{\lambda}{(1-\lambda)|s|} \bar{y}_0 \quad , \tag{1.26}$$

$$\bar{y}_2 = \frac{1}{2}\left[\frac{\lambda}{(1-\lambda)|s|}\right]^2 \bar{y}_0 \quad , \tag{1.27}$$

$$\bar{y}_3 = \frac{1}{3!}\left[\frac{\lambda}{(1-\lambda)|s|}\right]^3 \bar{y}_0 \quad , \tag{1.28}$$

$\ldots$

Hence equation (1.21) gives

$$\bar{y}_0\left[1+\frac{\lambda}{(1-\lambda)|s|}+\cdots+\frac{1}{r!}\left\{\frac{\lambda}{(1-\lambda)|s|}\right\}^r+\cdots\right]=1 \quad . \tag{1.29}$$

So long as r is less than $\sim 1/|s|$ the terms of the series are as in (1.29), namely the terms in the expansion of exp $[\lambda/(1-\lambda)|s|]$. To an adequate approximation we have

$$\bar{y}_r = \frac{1}{r!}\left[\frac{\lambda}{(1-\lambda)|s|}\right]^r \exp\left[-\frac{\lambda}{(1-\lambda)|s|}\right] \quad , \tag{1.30}$$

which is just the Poisson distribution for average value $\lambda/(1-\lambda)|s|$. This is the number of defects possessed by an average member of the population, giving a reduction of fitness by

$$(1-|s|)^{\lambda/(1-\lambda)|s|} \cong \exp\left[-\frac{\lambda}{(1-\lambda)}\right] \cong \exp -\lambda \tag{1.31}$$

compared to the initial state of affairs, the factor exp $-\lambda$ being to the first order in λ. [It will be recalled that terms of order λ^2 were omitted already in the differential equations (1.13) to (1.15).] The result, equation (1.31), is analogous to one obtained long ago by J.B.S. Haldane for a bisexual population.

The case $q \neq 0$ leads in a similar way to

$$\bar{y}_r = \frac{1}{(r-q)!}\left[\frac{\lambda}{(1-\lambda)|s|}\right]^{r-q} \exp\left[-\frac{\lambda}{(1-\lambda)|s|}\right] \quad , \tag{1.32}$$

for $r \geq q$, again the Poisson distribution of average value $\lambda/(1-\lambda)|s|$, but with the values of r pushed q places along. Writing $r = q + k$, we have

$$\bar{y}_0 = \bar{y}_1 = \quad \cdots \quad = \bar{y}_{q-1} = 0 \quad ,$$

$$\bar{y}_{q+k} = \frac{1}{k!}\left[\frac{\lambda}{(1-\lambda)|s|}\right]^k \exp\left[-\frac{\lambda}{(1-\lambda)|s|}\right] \quad , \quad k = 0,\ 1,\ 2, \ldots \tag{1.33}$$

The parameter q simply changes the zero-point from which the number of defects is counted, with $q = 0$ the least bad situation for the species. The boundary condition equation (1.16) defined $\bar{y}_0$ as the first nonzero fraction, requiring zero-point $q = 0$. If the boundary condition had been $y_0 = y_1 = 0$, $y_2 = 1$, $y_3 = y_4 = \ldots = 0$, $\bar{y}_2$ would have been the first nonzero fraction and $q = 2$ would have been the appropriate zero-point.

Why is it, one can wonder, that natural selection is able to prevent a situation in which the average individual has a fitness lowered by exp $-\lambda$ from worsening any further, when natural selection could not prevent the original situation from worsening, an original situation with all individuals having a higher fitness? The answer is that in the original situation with $y_0 = 1$, natural selection had nothing to operate on, nothing to bite on. Every population member was equal with nothing to choose between them. Only after mutations had produced a statistical distribution of defects represented by the Poisson distribution with average value $\lambda/(1-\lambda)\,|s|$ (i.e., $\lambda/|s|$ to the first order in λ) was there a sufficient separation between lucky and unlucky individuals for natural selection to hold the position from further decay. To appreciate the situation mathematically, consider the case $q = 0$. To the first order in λ we have

$$\bar{y}_r = \frac{1}{r!}\left(\frac{\lambda}{|s|}\right)^r \exp\left(-\frac{\lambda}{|s|}\right) \quad , \quad r = 0,1,\ 2, \ldots \quad . \tag{1.34}$$

With this distribution and if no further deleterious mutations were occurring, the average number of defects in the next generation would be given by

$$\frac{\alpha \sum_r r \frac{(1-|s|)^r}{r!}\left(\frac{\lambda}{|s|}\right)^r \exp\left(-\frac{\lambda}{|s|}\right)}{\alpha \sum_r \frac{(1-|s|)^r}{r!}\left(\frac{\lambda}{|s|}\right)^r \exp\left(-\frac{\lambda}{|s|}\right)} = \frac{\lambda}{|s|} - \lambda \quad . \tag{1.35}$$

Instead of each generation transmitting its own average $\lambda/|s|$ of defects to the next generation, selection, in the absence of new mutations, operates to reduce the number by λ, which of course is just compensated by the new mutation rate. Once the y_r values have evolved according to our differential equations to give the Poisson distribution (1.34), the situation is held in balance from generation to generation by natural selection. The present analysis brings out the important point that natural selection is not a promoter of what is good in any absolute sense. Natural selection can only favour what is better against what is worse. We should also notice that the cause of the decline of fitness exp $-\lambda$ was the egalitarian specification of the initial conditions (1.16). It was the utopian nature of (1.16), with every member of the population without defects, that caused the decline. If the initial state of affairs had possessed the same measure of elitism as the Poisson distribution (1.34), there would have been no decline.

For the explicit case $\lambda = 0.3$, $|s| = 0.01$, the average population member has 30 defects. The variance is therefore 30, and it is by natural selection favouring individuals with defects less than the average by $\sim(30)^{1/2}$, compared to individuals with $\sim(30)^{1/2}$ defects above the average, that natural selection holds back the flood of bad mutations. When for $|s| << 1$ the average number of defects is large, the Poisson distribution can be replaced by a continuous Gaussian form

$$\sqrt{\frac{|s|}{2\pi\lambda}} \exp\left[-\frac{|s|}{2\lambda}\left(x - \frac{\lambda}{|s|}\right)^2\right] dx \tag{1.36}$$

giving the probability of an individual possessing between x and $x + dx$ defects. It can be verified that (1.36) remains unchanged to the first order in small quantities if multiplied by $[1-|s|]^{x-\lambda/|s|}$ and if x in the exponential is replaced by $x - \lambda$. This invariance represents the effect of passing from one

generation to the next, with the shift of x caused by the appearance of new defects and $[1 - |s|]^{x - \lambda/|s|}$ the selection factor appropriate to an individual with x defects. As new defects arise, the distribution (1.36) maintains itself due to the x-dependence of the selection factor, with the following interesting consequence.

Suppose the individuals in any generation to be given distinctive names and suppose each offspring to be thereafter given its parent's name. As time goes on, the descendants of parents with x initially less than $\lambda/|s|$ become increasingly common at the expense of those with x initially greater than $\lambda/|s|$. Indeed, in the limit all individuals come to have the same name, that of the ancestor of least x (or if fluctuations in the incidence of mutations is included, one or other of the ancestors of smaller x). One line from among many starters eventually dominates the population.

When favourable mutations of the same $|s|$ are also considered to occur, but at a rate much less than λ, the effect is only to produce slight perturbations of the Poisson distribution (1.34), perturbations that are soon stamped out under the continuing pressure of the bad mutations. Favourable mutations become swallowed in the flood of bad ones, as was already noted above, so that systems which follow a single parent-to-offspring model cannot evolve in a Darwinian sense. The best that can be done is to hold the position, which is basically what bacteria have done for almost 4000 million years.

Two points of principle are worth emphasis. The first is that the usually supposed logical inevitability of the theory of evolution by natural selection is quite incorrect. There is no inevitability, just the reverse. It is only when the present asexual model is changed to the sophisticated model of sexual reproduction accompanied by crossover that the theory can be made to work, even in the limited degree to be discussed in Chapter 6. This presents an insuperable problem for the notion that life arose out of an abiological organic soup through the development of a primitive replicating system. A primitive replicating system could not have copied itself with anything like the fidelity of present-day systems (on which the estimate $\lambda \cong 0.3$ depends). With only poor copying fidelity, a primitive system could carry little genetic information without λ becoming unbearably large, and how a primitive system could then improve its fidelity and also evolve into a sexual system with crossover beggars the imagination.

The second point is that bacteria break out of a binary fission asexual model on occasion. The device is for a gene to be copied out of the circular DNA structure of a bacterium, for the separated gene known as a plasmid to leave its parent cell, and for it to invade some other bacterium, which need not be of the same species. The invaded bacterium may then insert the incoming plasmid into its own DNA, with the result that the usual invariance of asexual lines is broken by a gene passing from one line to another, a process with some of the mathematical aspects of the crossover process in sexual reproduction. By this means a favourable mutation is not irrevocably tied to all the bad mutations in the cell in which it arises. And by plasmid transfer from one bacterial species to another, individual species are not closed systems. The departure from the neo-Darwinian assumption that species are closed is crucial, for in open systems evolution can be made to work as the biological evidence suggests that it must work.

The existence of the phenomenon of plasmid transfer, and the circumstance that the usually quoted examples of bacterial evolution are associated with it, can give us confidence that our mathematical deductions are correct. For if evolution by natural selection really worked in the abstract sense in which neo-Darwinians assert that it works, then there would be no need for plasmid transfer.

As well as suffering from an inability to profit from favourable mutations, the binary fission and budding models are subject to an insidious erosion process arising from environmental fluctuations, the same one-way street we encountered earlier. To illustrate this property once again, suppose an environmental fluctuation wiped out all individuals with values of r above the average $\lambda/|s|$ in the Poisson distribution (1.34), leaving individuals with fewer than the average number of defects unaffected. With too little for natural selection to bite on, the resulting improvement of the species could not be held by natural selection against the pressure of deleterious mutations. Instead of the boundary condition (1.16), we would have a new problem with a different boundary condition, but one which suffered like (1.16) from having too many fit individuals for its own good. Like (1.16), deleterious mutations would accumulate until the Poisson distribution (1.34) reasserted itself. Consider next the opposite case in which some revolutionary maniac wipes out the more fit individuals, guillotining those with less than $\lambda/|s|$ defects. Once again, nature finds too little diversity among the remaining individuals, so that more bad mutations accumulate until a Poisson

distribution, but now the Poisson distribution

$$\bar{y}_{r+\lambda/|s|} = \frac{1}{r!}\left(\frac{\lambda}{|s|}\right)^r \exp\left(-\frac{\lambda}{|s|}\right) \quad , \quad r = 0,\ 1,\ 2,\ \ldots \quad , \qquad (1.37)$$

the solution of equations (1.13) to (1.15) to the first order in λ for the case $q = \lambda/|s|$. All the y values for defects up to $\lambda/|s| - 1$ necessarily remain zero since, exceedingly rare inverse mutations apart, there is no means of recovering individuals with less than $\lambda/|s|$ defects. Because of the guillotine such individuals have gone forever.

Fluctuations of the environment have just such a pernicious effect, with the Poisson distribution getting pushed steadily to higher and higher values of q. There is a component of environmental fluctuation that wipes out individuals without regard to their genetic quality. The accidental wiping out of the genetically unfavoured does no permanent good, but the accidental wiping out of the genetically favoured does permanent harm. Suppose (1.34) to become established for the case $q = 0$, $\lambda/|s| = 30$. The numbers of individuals with 0, 1, 2, 3, 4, and 5 defects in such a distribution is small, so small as to be exposed to accidental extinction. Once this happens, in not many generations a combination of mutations and natural selection will tend to move the Poisson distribution toward $q = 5$, with all members of the population coming to possess ~5 extra defects. This erosion process continues indefinitely as time goes on, smoothing itself instead of going in jerks, with the distribution of defects always tending toward a Poisson distribution, but never quite reaching it as the truncation at lower values of r progresses. Taking the truncation rate reasonably to be one individual per generation, I estimate an increase of q with time determined by an equation of the form

$$\frac{dq}{dt} \approx \left(\frac{\lambda^2}{N|s|}\right)^{\frac{1}{2}} \quad , \qquad (1.38)$$

so that the average fitness declines in G generations by the factor

$$\sim(1-|s|)^{G\lambda/(N|s|)^{\frac{1}{2}}} \quad , \qquad (1.39)$$

which is to say e^{-1} in

$$G \cong \left(\frac{N}{\lambda^2|s|}\right)^{\frac{1}{2}} \qquad (1.40)$$

generations. For a mammalian species with $N = 10^6$, $\lambda = 0.3$, $|s| = 0.01$, (1.40) is about $3 \cdot 10^4$ generations, far too short for any mammalian species to reproduce successfully by budding or by binary fission over a time scale of $\sim 10^7$ generations.

Bacteria, which do reproduce largely in accordance with the present model, have unusual properties that enable them to resist deleterious erosion through environmental fluctuations. First, the amount of bacterial DNA is less by an order of magnitude or more than the amount of operational DNA in mammals (taken above to be $\sim 10^8$ base pairs), so that for similar copying efficiencies, λ is an order of magnitude less. Second, bacteria tend to reproduce in explosive exponential bursts, followed by slow declines of population with the cells adopting a defensive nonreproductive resting state, so that they die only very slowly. Unless conditions are favourable for replication, the tendency is thus to fall into an extreme state of hibernation, in which life persists without consuming much in the way of resources. Outside the artificial conditions of a laboratory where bacteria can be made to reproduce continuously, the bacterial population tends to follow a sawtooth pattern, with sudden jumps followed by slow declines. Since there is little or no replication during the lengthy declines, the system is extremely economical in the number of reproductive steps which it employs. Only 1000 generations employed exponentially with one making two, two making four, four making eight, ... , yields a factor of increase exp1000, which would provide for the rises involved in many "teeth" of the "saw," say exp10 in 100 "teeth," with long resting intervals between. So can a bacterial population withstand the degenerative erosion discussed above, and only so, I would

think. That bacteria evade the need to maintain a parent-to-offspring chain through an immense number of generations is again indicative of the correctness of the mathematical argument. Eucaryotic organisms often form spores, which appear to be devices for going into a resting state, and this yet again supports the mathematical argument. Simple eucaryotic organisms often have sexual cycles in addition to their more usual budding mode. Such cycles seem odd when viewed empirically, especially when the curiously varied details in which the cycles operate are considered. But viewed mathematically, sexual cycles are essential, otherwise continuing genetic erosion over many generations would lead to eventual disaster.

Two aspects of the genetic system in higher animals require special consideration: mitochondria derived only from the female parent and the Y chromosome present only in males. Mitochondria contain comparatively little DNA, and reducing the amount from the $\sim 10^8$ base pairs of the above discussion to $\sim 10^5$ would increase our previous estimate of $3 \cdot 10^4$ generations as the erosion interval to $\sim 3 \cdot 10^7$ generations, which would be tolerable.

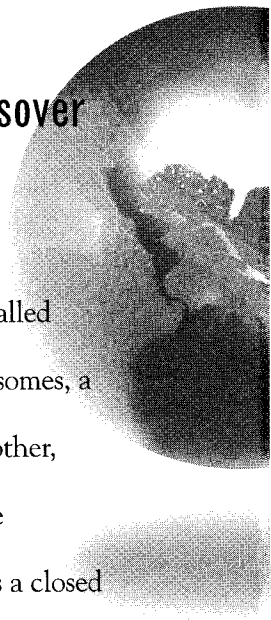
The two chromosome sets in humans are 46 in total number, forming 23 pairs of which one pair is sex-determining. That in females has two similar so-called X chromosomes but the sex-determining pair in males has one X chromosome together with a smaller Y chromosome. The X chromosomes experience crossover when female gametes are produced. Hence genes on the X chromosomes are protected according to the point of view to be developed in Chapters 2 and 3. Genes carried on the Y chromosome are not usually considered to interchange with genes on the X chromosome, however. Genes on the Y chromosome follow the male line of inheritance, essentially as in the single parent-to-offspring model considered above. This view has recently been challenged by some biologists, who have claimed that Y chromosome genes do indeed interchange with X chromosome genes. If all did, it would be difficult to understand what aspects it is of the Y chromosome that generates the characteristics of maleness, since females would then possess every gene possessed by males. I will therefore suppose the orthodox position to be correct on this point, at least to the extent that some fraction of Y chromosome genes follow the single parent-to-offspring model.

If effectively all the Y chromosome genes are taken to follow the single parent-to-offspring model, and if the Y chromosome were of average length with, say, $5 \cdot 10^6$ expressed base pairs, the degeneration interval given by (1.40) would be some 20 times longer than the estimate $\sim 3 \cdot 10^4$ generations

obtained above for $\sim 10^8$ base pairs, that is, $\sim 6 \cdot 10^5$ generations, which would be consistent with the last stages in the evolution of the upper primates, but considerably short of the entire span of mammalian evolution.

Chapter 2

Cell Division and Crossover



The body cells of an organism, the so-called somatic cells, possess two sets of chromosomes, a set *P* from the father and *M* from the mother, reproduction being now bisexual. Unlike bacteria whose single chromosome forms a closed loop, chromosomes in fungi, plants, and animals are linear gene-bearing segments consisting of coiled double-stranded DNA with its multitude of base pairs carrying the genetic inheritance of

the organism in question. Each parent contributes the same number of chromosomes—typically about 25 in mammals—so that in the somatic cells there are about 50 chromosomes, present in the nuclear region surrounded by a protective membrane.

The sets P and M can be arranged in pairs in such a way that, excepting a sex-determining pair which requires separate consideration, the two chromosomes of a pair are similar to each other—homologous it is said—whereas chromosomes in different pairs are quite dissimilar. It will be useful to denote a pair of similar chromosomes by (p, m), p being from P and m from M. The totality of chromosomes normally present in somatic cells will be denoted by (P, M). Biochemical processes in a cell are such that similar pairs (p, m) can find each other, as they do during the process of division which leads to the formation of sex cells.

The sex-determining chromosome pair is homologous in females, (X_p, X_m) say, with X_p derived from the male parent and X_m from the mother. In male mammals, on the other hand, the two chromosomes of the sex-determining pair, (Y_p, X_m) say, are very different, with Y_p coming form the father and X_m from the mother.

The first step in the production of either body (somatic) cells or sex cells (gametes) is a doubling of both P and M. This occurs immediately before the intricate maneuvers of cell division begin, so that a cell on the threshold of division contains four sets of chromosomes, $(2P, 2M)$. The production of somatic cells is analogous to the binary fission model studied in the previous chapter, namely

$$(2P, 2M) \rightarrow (P, M) + (P, M) \quad . \qquad (2.1)$$

The production of gametes is something quite different, however. But before coming to it, let us not pass (2.1) without indulging in an aside. Since (2.1) is like the model of the previous chapter, we can ask if the ideas of the previous chapter apply with respect to the number of cell divisions that can pass before copying errors destroy the fidelity of the system, leading to aging and senescence of the organism.

We have to conceive here, however, of the additional possibility that many copies are run off from a single master cell. So long as the master cell remains undamaged, the copies would get no worse with time, and aging should not occur. Yet almost surely master cells do degenerate and have

themselves to be replaced from time to time. In such a situation it would be the replacement of master cells that defined the passage of "generations" in the sense of the previous chapter. The many ordinary cells start as copies from the masters would be like juveniles who did not survive to maturity. At the same error rate as before, $\lambda \cong 0.3$ per replication of one chromosome set, an appreciable fraction of replacements introduce a defect. If master cells were to pass by title like kings in a dynasty from one generation to another without selection, then defects add up cumulatively. However, because each cell has two chromosome sets only defects of the dominant type—those which are expressed when on one chromosome set—will be relevant. This is because it is most unlikely that a defect will occur to the same gene in both P and M. While the protection thus given by two chromosome sets is a positive factor, the value $s = -0.01$ given to all defects in Chapter 1 was surely low, at least for some defects, which is a compensating negative factor. Aging proceeds more or less linearly with time at first, as would be expected from a steady accumulation of defects, but eventually a stage is reached where an aging organism appears to fall over a precipice, as would inevitably be so should defects begin to destroy the efficiency of the copying process itself, when severe deleterious feedback would set in, with defects generating more defects at an increasing rate and with the copying process failing to operate at all in the ultimate limit.

A logical device one can think of for arresting the aging process is actually adopted in practice, which adds to one's confidence that the line of argument is correct. The device is to employ cells for special functions in the organism, differentiation as it is called. In such an arrangement, defects involving one function need not involve another function. So far as any particular function is concerned the effect is to reduce the error rate and hence to prolong the length of time for which an organism can exist without serious decline taking place. In such an arrangement the function that will decline soonest will be the one requiring the greatest amount of genetic information, which for mammals is probably the operation of the brain, a circumstance that might explain why some experts on geriatrics maintain that aging spreads from the brain, and currently many people become set in their ways mentally long before the physical abilities of the body undergo decline.

Be this as it may, the empirical fact that the degeneration of the somatic cells occurs in not more than a few tens of generations emphasizes the amazing ability of species to preserve information in the sex cells over

millions of generation, and, according to the Darwinian evolutionary theory, not just to maintain the integrity of the genetic information but even to improve it. The aging process shows very clearly that the caution expressed in the previous chapter was not misplaced. The mere existence of the aging process shows, indeed, that statements one frequently hears, to the effect that the Darwinian theory is as obvious as the Earth going around the Sun, are either expressions of almost incredible naiveté or they are deceptions. Since, according to the general theory of relativity, it needs some sophistication to give meaning to the statement that the Earth goes around the Sun, naiveté is the more probable explanation. Even so, with such widespread evidence of senescence in the world around us, it still seems amazing that so many people think it "obvious" that the biological system as a whole should be headed in the opposite direction, traveling from inferior to superior, traveling as it were from age to youth.

Although one often hears that the cells which divide by the highly complex process of meiosis to give sex cells also undergo an aging process, aging if it exists is certainly a much lesser effect than the decline of the somatic cells. This means that a certain master copy or copies of the earliest (P, M) cells must still be retained substantially without loss of genetic integrity. The children of parents with graying hair do not grow gray hair, proving that unimpaired genes for the production of hair are still present in the parents, although the parents have no means of using them for their own hair. The world is full of quack recipes for stopping and reversing the aging process. When a recipe has an actively harmful effect—as is the case with the Far Eastern consumption of rhinoceros horn, which is currently leading to the virtual extinction of the rhinoceros—it is to be deplored, exposed, and stamped upon. Otherwise such recipes are merely hilarious. The one recipe which conceivably might be successful would be to read pristine genetic information from the progenitor cells of gametes into the production of somatic cells, as for instance gray-haired parents might make use themselves of the pristine hair-producing genes which they are able to confer on their children. Even this recourse would not be completely effective, however, if in aging people the master program whereby cells are organized as a whole has become defective. But experience with computers shows that master programs are often quite short compared with the subroutines they control. If the same were true biologically, a long time interval could elapse before defects showed up in the basic controlling processes within an organism. A considerable

slowing of the aging process might then be possible, which was something that centuries ago was supposed to be achieved by mystic rites, or in the case of Dr. Faustus, by selling one's soul to the devil. Oddly enough, the means of achievement probably lies in all of us, but like the graying parents we cannot make use of our own inner store of inviolate genetic information.

This ends my aside on the aging process. In crossover, a p chromosome exchanges a piece of itself with a corresponding piece of an m chromosome. Immediately before cell division, it will be recalled, the chromosome sets double to $(2P, 2M)$, which can be arranged into a number of quartets $(2p, 2m)$. Although the possibilities for crossover in a quartet are wide, the two p chromosomes are said not to exchange pieces, and neither do the two m chromosomes, but either or both of the p chromosomes can exchange a piece or pieces with either or both the m chromosomes. Where an exchanged piece includes the end of a chromosome, the exchange is achieved by a single crossover made at homologous points—that is, at positions with the same relation to the genes on the interlinked chromosomes. Where an exchanged piece is internal there are two crossovers between the same p and m chromosomes. Consider as an example the case in which an exchanged piece is internal between one p and one m, the other p and m remaining unchanged. Then the p and m involved can be thought of as each broken into three pieces

$$p \rightarrow p' + p'' + p''', \quad m \rightarrow m' + m'' + m''' \quad , \tag{2.2}$$

with p' and m' homologous, p' and m'' homologous, and p''' and m''' homologous. Now join up the pieces but with p'' and m'' exchanged, giving the resultant effect

$$p, m \rightarrow p' + m'' + p''', \quad m' + p'' + m''' \quad . \tag{2.3}$$

The quartet $(2p, 2m)$ therefore becomes

$$(p, \ p' + \underline{m}'' + p''', \ m' + \underline{p}'' + m''', m) \quad , \tag{2.4}$$

the underlined segments being those which have been exchanged.

Subsequent division of the cell containing the quartet (2.4) are controlled by an organizational region on each chromosome known as the centromere,

which for definiteness will be taken to lie in the exchanged pieces. The first cell division then gives

$$(p, p' + \underline{m}'' + p''', m' + \underline{p}'' + m''', m) \rightarrow (p, m' + \underline{p}'' + m''') + (p' + \underline{m}'' + p''', m) \quad , \tag{2.5}$$

the two pairs on the right-hand side of (2.5) being the genetic contents of the two daughter cells, the empirical rule in what I have read apparently being that the two paternal centromeres go together as do the two maternal centromeres. Each of the daughter cells in (2.5) then goes into two further cells,

$$(p, m' + \underline{p}'' + m''') \rightarrow (p) + (m' + \underline{p}'' + m''') \quad , \tag{2.6}$$

$$(p' + \underline{m}'' + p''', m) \rightarrow (p' + \underline{m}'' + p''') + (m) \quad , \tag{2.7}$$

so that the original quartet $(2p, 2m)$ has divided and subdivided after crossover into four cells each containing a single chromosome, which may be either the original p or m coming through unchanged, or the mixtures $(p' + \underline{m}'' + p''', m' + \underline{p}'' + m''')$ of the original p and m. It is also possible that more complex mixtures are formed with both p chromosomes exchanging pieces with both m chromosomes.

Returning to the full complement $(2P, 2M)$ existing immediately before meiosis, there are many quartets $(2p, 2m)$ and no consistent pattern occurs in crossover between one quartet and another, the pieces exchanged in different quartets being different. Nor in the two successive cell divisions is there a consistent pattern as to which of the four possibilities from each quartet goes to a particular gamete. Hence the possibilities for variation are immense, with the parental genes being shuffled to an amazing degree in only a single meiosis. When all the gametes produced by an individual are taken together, the shuffling attains a considerable fraction of the immense possibilities for variation that exists between the chromosome sets P and M.

Notice that shuffling takes place within each separate individual, not when male and female mate to produce an offspring. The latter has (P, M), with P the particular male gamete and M the female gamete that happen to come together. It is P and M separately which have been shuffled. From the

point of view of the offspring, it is the paternal grandparents' genes which are shuffled in P and the maternal grandparents' genes in M. Shuffling is two generations back from the present generation. In the shuffling process half the genes which our grandparents transferred to our parents have been discarded. Viewed from the point of view of grandparents, no immediate mixing of genes occurred in their immediate children. Mixing occurred in the grandchildren, which is perhaps why the relation between children and their grandparents is so clearly different from the relation with their immediate parents. In a genetic sense nothing is really achieved between male and female until, in the second generation, their grandchildren are born.

In a randomly mating population, genes circulate very rapidly indeed. In order to make the following statements more precise rather than for any reason of principle, let us omit selective factors for the moment. Also let the population N remain stable from generation to generation and posit a highly egalitarian society in which every individual is a parent of two surviving offspring. Consider the old paradox. Each individual in the present generation has 2 parents, 4 grandparents, 8 great-grandparents, and so on back to 2^G ancestors G generations ago. But for $G > (\ell nN/\ell n2)$, the number of ancestors on this reckoning exceeds N, which is impossible. The error lies of course in the implicit assumption that all ancestors are different. One can think of a genealogical tree in a reversed time sense, with two branches back into the previous generation from any individual, with four branches into G = 2, eight branches into G = 3, and 2^G branches in general. When $G << (\ell nN/\ell n2)$, there will not usually be a path among the branches going back from the individual in question to a particular individual existing in the population G generations ago. When $G \cong (\ell nN/\ell n2)$, however, there is usually a path going from any individual in the present generation to any particular individual in the population G generations ago. After $G \cong (\ell nN/\ell n2)$ generations, most individuals in the current population have ancestors in common, while for $G >> (\ell nN/\ell n2)$ there are many paths connecting any individual today to any specified individual G generations ago, counting paths among the branches as being different if they have any sequences of generations that are different.

$G = (\ell nN/\ell n2)$ is a remarkably short number of generations, for $N = 10^6$ only about 20 generations. Taking a human generation to be 20 years, in only four centuries a population of a million individuals who mate at random become related to each other. Increasing N to 10^9 individuals only

increases the mixing time to six centuries. This makes nonsense of the highly restricted family connections of which so many people are intensely proud. By separating out a small fraction of N and by restricting mating to individuals within the small fraction, a tighter "family" can of course be achieved. Through deliberate mate selection aristocratic families and castes can be created, with the terrible genetic consequences to be considered in Chapter 5.

Suppose there are ~5000 genes to a chromosome, with about $2 \cdot 10^5$ genes in all is (P, M). After $G = (\ell nN/\ell n2)$ generations, the average expectation for the number of genes that we have received from each individual who existed G generations ago is $\sim 2 \cdot 10^5/N$, which for $N = 10^6$ is only 0.2. This tells us that most of the genealogical paths linking us to our distant ancestors carry no genes. Although the paths actually existed, with an actual offspring being born for every link of a path from one generation to the next, most paths carry no genes. This is because half the genes of its grandparents are lost whenever an offspring is born. If we denote present-day individuals by $I_1, I_2, \ldots, I_N$, and those which existed G generations ago by $I_1(G), I_2(G), \ldots, I_N(G)$ a path connecting I_j to $I_k(G)$ becomes less and less likely to carry genes, and so to be a genetically relevant ancestral connection, as G increases toward $\ell nN/\ell n2$. Most of the paths from a particular present-day individual I_j to $I_1(G), I_2(G), \ldots, I_N(G)$ carry no genes but there is an occasional path that carries a whole block of genes, thereby enabling the average value of genes per path to be 0.2.

It is easy to estimate the size of the occasional gene block received from an ancestor of $G = (\ell nN/\ell n2)$ generations ago. Starting with the chromosomes as they were G generations ago, and supposing one crossover per chromosome per generation, there will have been G breakage points, so that crossover will have the effect of chopping the earlier chromosomes into G pieces, each with ~(5000/G) genes. For G = 20, this is ~250 genes. Thus, occasionally, from one of our ancestors of 20 generations ago—an ancestor at random—we inherit two or three hundred genes, and from the overwhelming majority of ancestors, nothing. This explains why the population seems so varied in its fine detail and why at first sight there seems to be no rhyme or reason in it.

From any assigned starting point, crossover divides the chromosomes into finer and finer pieces (which are, of course, constantly being reassembled) as time goes on. After ~5000 generations the pieces become of the order of a single gene, with the entire gene associations one with another changed from

what they were at the start. For humans this is approximately the length of time back to the emergence of Crô-Magnon man, the usually supposed ancestor of modern humans. Taking $N \cong 10^4$ in Crô-Magnon times, we would therefore have $\sim 2 \cdot 10^5/N \cong 20$ genes from each of our Crô-Magnon ancestors. Unlike the situation $(\ell nN/\ell n2)$ generations ago, for which we have no genetic connection to most of our ancestors by birth, we have, oddly enough, a rather uniform connection to our really distant ancestors. This is achieved through the immense multiplicity of paths that arise for G large. Most paths again carry no genes, but the great number of them connecting I_j to any $I_k(G)$ additively produce an average of a few genes. This is when G becomes so large that crossover has chopped up the original chromosome into very fine pieces.

To summarize a curious situation, we each have a strong genetic connection to our immediate forebears and to recent ancestors shown in the family trees, which people are anxious to know about to the extent that constructing family trees for others can be quite a profitable line of business. Experience shows that after a handful of generations such trees become impossibly diffuse if they are at all complete. Professionals in the business then miss off-branches by the dozen. Since loped-off branches could be just the ones that carry blocks of genes, the trees become biologically meaningless. After only a few generations precise detail therefore becomes lost, and we have to look instead to averages. Although the average English person today has parent-to-child paths going back to a considerable fraction of the inhabitants of Tudor England, most such connections have no genetic significance. Some do, however, with considerable blocks of our genes being derived from individuals whose identities are unknown to us—the individuals could just as well be Shakespeare or Henry VIII as anyone else. Curiously enough, the chance of an explicit genetic connection existing to an inhabitant of Roman Britain is greater than to an individual of Elizabethan times, while for still greater time spans back into the Stone Age, the chance becomes greater still and, ultimately, for our distant Crô-Magnon ancestors becoming high. An outsider who observed the passage of events over a time scale of tens of thousands of years would probably think of us not as distinct individuals but as one creature, rather as, genetically, we may think of a swarm of bees as just one bee. I am surprised that Christians do not use this consideration as an argument in their favour, for it adds logic to the ethic of treating your neighbour as yourself.

It will be recalled that the average number of defects possessed by an individual for the single parent-to-offspring model studied in Chapter 1 was $\lambda / |s|$, where λ was the rate of occurrence of defects per individual per generation and $s < 0$ was the selective penalty imposed by each defect, taken all to be of the same severity. The numerical values considered in Chapter 1 were $\lambda = 0.3$, $|s| = 0.01$, for an average of 30 defects, which is similar to the number of chromosomes found typically in the cells of plants and animals. Crossover apart, the random choices at meiosis of whole chromosomes, with a gamete sometimes getting a p chromosome and sometimes an m chromosome from the P and M sets, already decouples a favourable mutation occurring on a particular chromosome from defects present on other chromosomes. Only defects on the same chromosome can therefore interfere with the penetration of a favourable mutation. With the number of defects per chromosome of order unity, a favourable mutation is already halfway free to show through the defects, even in the absence of crossover. This no doubt is the reason why the genetic material of plants and animals is indeed fragmented into an appreciable number of segments which can be treated independently of each other at meiosis—instead of being present essentially as a whole as in bacteria. Defects with $|s| > \sim 0.01$ are largely coped with by multiple chromosomes.

Crossover permits a still finer gradation, which is to say a decoupling appropriate to smaller selection factors than those studied in Chapter 1. A similar analysis to that of Chapter 1, but for $|s| = 0.0001$ and with the same $\lambda \cong 0.3$, would lead to the average individual possessing $\sim \lambda |s| = 3000$ defects with ~100 present on each chromosome. If favourable mutations with $s = 0.0001$ are to show through so large a number of adverse mutations a system for dividing chromosomes into pieces less than one percent of their length and of then reassembling them randomly is necessary. This is just what crossovers operating for upward of 100 generations succeed in doing. A few divisions occurring in each generation, effected by the device of exchanging pieces between a p and an m chromosome, does the job splendidly provided the exchanged pieces are randomly chosen at each generation, which appears to be the situation.

It is a fair inference from the existence of crossover and from the shifts to which both plants and animals go in order to maintain sexual reproduction—shifts ranging from the devices of plants to secure cross-pollination by insects, to the pheromones employed by insects themselves, to the gaudy

fantail of the peacock, and of course to human examples of which there is essentially no limit—that positive evolution must turn on minute advantages with $s \cong 10^{-4}$ or even less. Otherwise, a simpler system would be sufficient, as for instance fragmenting chromosomes into smaller pieces, or micro-chromosomes, such as are actually found in birds and reptiles. The latter system, apparently not being sufficient, was abandoned in mammals.

To add mathematical substance to what has just been said, consider a situation like that studied in Chapter 1 in which natural selection checks the flood of deleterious mutations from overwhelming a species. This can only be done, as we saw in Chapter 1, through the random incidence of mutations setting up fluctuations in their number between one individual and another. Natural selection then distinguishes between those individuals with fewer and those with more than the average number, μ say, of defects. If the adverse mutations all have the same $|s|$, the balance imposed by natural selection follows the Poisson distribution according to which

$$\frac{\mu^k}{k!} \exp -\mu \tag{2.8}$$

is the probability of an individual at random having k defects.

Suppose now that a favourable mutation of selective advantage $S > 0$ is possessed by a fraction x of the population, and suppose the favourable mutation to be uncorrelated with the defects, by which is meant that individuals with or without the favourable mutation have the probability (2.8) of possessing k defects. The problem is to determine how x varies from one generation to the next, the population being constrained by the environment to stay fixed.

In a sexual system with the double set of genes (P, M), there are three possibilities for a favourable mutation—it may be present on one or other of P and M, it may be present on both, or it may be present on neither. Since in later chapters these three possibilities will be treated in detail, it is sufficient here to simplify them to two—either an individual possesses the favourable gene and so enjoys a selective advantage $1 + S$, or not. The number of surviving offspring for an individual with k defects and with the favourable mutation can then be written as $\alpha(1 + S)(1 - |s|)^k$, while an individual with k defects but without the favourable mutation leaves an

average of $\alpha(1-|s|)^k$ offspring who survive to maturity, where α is a normalizing factor chosen so that the population remains fixed, that is to say

$$\alpha\left[x(1+S)+(1-x)\right]\sum_{k=0,1,2,\ldots}(1-|s|)^k\frac{\mu^k}{k!}\exp-\mu \;=\; 1 \qquad .(2.9)$$

Using the same method as in Chapter 1 to obtain dx/dt, we have

$$x+\frac{dx}{dt} \;=\; \alpha x(1+S)\sum_{k=0,1,2,\ldots}(1-|s|)^k\frac{\mu^k}{k!}\exp-\mu \qquad , \quad (2.10)$$

whence

$$x+\frac{dx}{dt} \;=\; \frac{x(1+S)}{1+Sx} \qquad , \quad (2.11)$$

that is,

$$\frac{dx}{dt} \;=\; S\frac{x(1-x)}{1+Sx} \qquad , \quad (2.12)$$

which is just the positive selection the favourable gene would have in the absence of the defects. If the Poisson distribution (2.8) were replaced by probabilities p_k, $\Sigma\, p_k = 1$, the result would be the same. The result depends only on uncoupling the favourable mutation from the defects.

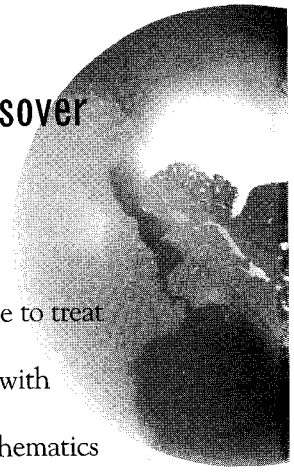
Just as it makes no difference if $\mu^k \exp - \mu/k!$ is replaced by p_k, it makes no difference to the derivation of (2.12) if $-|s|$ in (2.9) and (2.10) is replaced by $|s|$. The advantageous mutation S is also selected independently of other advantageous mutations, which means that advantageous mutations select in parallel with each other, instead of only sequentially as one would have for the model of the previous chapter if one were to somehow be rid of the more frequent deleterious mutations in that model. If in the single parent-to-offspring model one had two advantageous mutations $S_1 > S_2 > 0$ in different

lines and no disadvantageous ones, the possession of S_2 could be viewed as a disadvantage compared to the possession of S_1. Hence, after lines without either mutation killed out, S_1 would proceed to kill out S_2. In the sexual model with crossover, on the other hand, S_1 and S_2 go their separate ways, so permitting both to be favoured selectively.

This latter advantage of sexual reproduction seems to be the strongest argument claimed in the books for it over the asexual model of Chapter 1. Fisher's *The Genetical Theory of Natural Selection* carries the point in the exquisite ellipticities that were so characteristic of Fisher. With quite some searching one can find it in Sewell Wright's treatise in four volumes, *Evolution and the Genetics of Populations* (University of Chicago Press, 1984) and more directly and clearly in J. Maynard Smith's *The Evolution of Sex* (Cambridge University Press, 1978). What one does not find, however, is an appreciation of the really crucial aspect of the matter, that only with sexual reproduction accompanied by crossover can positive mutations make headway against the deleterious mutations which occur with far greater frequency, and which otherwise would swamp the advantageous mutations, not permitting them to make any headway at all.

Chapter 3

A Bisexual Model with Crossover



The immense simplification of being able to treat genes independently in a bisexual model with crossover permits more sophisticated mathematics to be used, mathematics that combines selection and stochastic effects within the same formalism. A word of caution first, however. On a broad perspective the selective factors contributed by different genes are interlinked. Where enzymes cooperate together in groups—for example, the

thirty or so enzymes with functions in the process of glycolysis, or the twenty or so cytochromes involved in the process of electron transfer—complicated functions of all the enzymes in a group affect the performance of an organism, rather as the performances of a soldier in battle depends on those who flank him as well as on his own inherent qualities. Yet, in what follows I shall consider the selective factors of genes to be independent of each other, and there are two reasons for doing so. There is no magic about the term "gene," and so far as the mathematics is concerned we can take a set of the kind just mentioned as acting together to form a kind of supergene, at any rate so long as the DNA for all the genes of the set are sufficiently adjacent to each other for them to be fragmented only rarely by crossover. The second reason is mathematical, namely that when selective factors are small compared to unity, as they are normally supposed to be in neo-Darwinian theory, even complex functions can be linearized by suitable expansions, much as potential functions in dynamics are linearized for small motions, even though they may depend on many coordinate variables.

To this point we have passed in a single step from one generation to the next, relating parents only to the minority of their offspring who survive to become parents themselves. This was done by writing $\alpha(1 + s)$ as the number of surviving offspring of a parent with some selective property A, compared to α alone for the number from a parent with the alternative property a, adjusting α so as to maintain a fixed population. The factor $1 + s$ was thus the relative "fitness" between individuals with A and those with a, a concept with meaning in relation to a specific environment. In general, "fitness" cannot be determined by genetics alone. Let A and a refer, for example, to the colouring of a female ground-nesting bird, with A giving camouflage against hawks in one geographical locality and a in another locality. The value to be assigned to s evidently depends on which locality is in question, with s switching sign from one to the other.

In addition to obvious physical factors such as water supply, soil content, or annual temperature range, the "environment" must cover not only the presence of other species but even subtle aspects of the species under consideration. Knowledge is a major part of the present-day human environment, for example. In the early human communities of 50,000 years ago even rather moderate gene defects must have been essentially lethal, $s \approx -1$, but with modern medical knowledge and with the emergence of compassionate societies, sufferers from such defects can nowadays reach reproductive age. Moreover, since sufferers

from some diseases tend to be hyperactive sexually, the appropriate value of s in such societies may become > 0, with a previously lethal handicap having become a biological advantage.

There is no single environment specifying a single set of genetic selective factors. Even at a particular moment the Earth offers an immense range of environments, and with respect to time the range is greater still. Moreover, the environment is capable of changing with dramatic suddenness. Hence our postulate of a fixed population maintained in a fixed environment relative to which selection takes place is a highly idealized concept. Or, more precisely, from a mathematical point of view we can think of the hypothesis of a fixed population in a constant environment as generating a neighbourhood solution. Neighbourhood solutions can be joined piecewise to obtain broader solutions, possibly with discontinuities in the derivatives of functions arising in cases of sudden environmental shifts.

Let us come now to the important question of how selection really operates. While it is sufficient to proceed from parents to surviving offspring with the aid of the normalizing factor α, much is thereby omitted. The herring is said to produce of the order of a million offspring for every one that survives to maturity. What is it that decides the minute fraction of individuals that survive to reproduce the next generation? The huge numbers of juvenile herring provide food for a great range of sea-dwelling plants and animals. The multitude of ways in which juvenile herring come to a sticky end—literally so where some plants are concerned—is a topic for the excellent nature films which are so justly popular on television. I have heard commentators imply that the herring parents were obliged to produce 1,000,000 juveniles to satisfy the appetites of predators in order that the latter will graciously permit one juvenile to grow to maturity. This has to be wrong. In a free-for-all, there is no way in which 999,999 juveniles are going to be consumed and the last one spared. The slightest additional snap of the jaws and the last one also will be gone. It has to be that somewhere in the environment there are safe niches that the predators cannot invade. When safe niches are known to parents, as they are for some species, the niches are purposively sought out. Where safe niches cannot be known to parents, the only recourse is to produce such an immense flood of juveniles that a few of them are certain to chance on the fortunate nooks and crannies.

Write N for the adult population, taking N to be constant from generation to generation. In the model to be studied below it will be

assumed that M juveniles are produced in each generation with M appreciably larger than N, and it will be further supposed that M is independent of N. Clearly this cannot be strictly true, since there can be no juveniles at all when $N = 0$. If N falls too low, a species cannot produce enough juveniles to exploit the niches available to it. In such circumstances the species becomes "endangered" as one says. But endangered species aside, so many juveniles are produced that we can conveniently take M fixed.

Let x_0 and $1 - x_0$ be the frequencies at time $t = 0$ of the alternative forms A and a of a particular gene, meaning that of the $2N$ sets of chromosomes possessed by the N individuals $2Nx_0$ have A and $2N(1 - x_0)$ have a. Omitting selection for the moment, what can we say of the frequency of A in the next generation, at $t = 1$, taking the generation interval as the unit of t? Let the N individuals mate at random, in which case any chromosome set possessed by any of the M juveniles in the next generation has a chance x_0 of carrying the A form of the gene, and the probability of the A form appearing $2rM$ times in the next generation will be the term in $p^r q^{2M-r}$ in the binomial expansion of $(p + q)^{2M}$, where $p = x_0$, $q = 1 - x_0$. Behind this random transmission of the A form is the consideration that each of the N individuals produces a supply of gametes even larger than M/N, with random mating of the N individuals interpreted as choosing their gametes at random, M female ones and M male ones, both having x_0 as the frequency of the A type gene. It is possible to define random mating in other ways that lead to results that are different in detail but not in principle.

Terms in the expansion of $(x_0 + \overline{1 - x_0})^{2M}$ can be approximated for $M >> 1$ by a Gaussian distribution of variance $2Mx_0(1 - x_0)$. The probability that the frequency of A lies between x and $x + dx$ among the M juveniles of the next generation is

$$\sqrt{\frac{M}{\pi x_0(1-x_0)}}\ \exp\left[-\frac{M(x-x_0)^2}{x_0(1-x_0)}\right]dx \qquad (3.1)$$

in this Gaussian distribution. This is provided x_0 is not close to the end points of the range $0 \le x \le 1$, and taking $M >> 1$ so that the integral of (3.1) over $0 \le x \le 1$ is essentially the same as over $-\infty < x < \infty$.

The M juveniles are reduced to N at maturity, with the ratio M / N highly variable from one species to another. Thus M / N is $\sim 10^6$ for the

herring but only ~5 for birds and for humans under primitive conditions. Without selection the reduction from M to N would again be at random, in which case the probability of the gene frequency lying between x_1 and $x_1 + dx_1$ among the N individuals at maturity would be

$$\sqrt{\frac{N}{\pi x(1-x)}}\ \exp\left[-\frac{N(x-x_1)^2}{x(1-x)}\right]dx \quad , \qquad (3.2)$$

should the gene frequency among the M juveniles happen to be x. The total probability of the gene frequency lying between x_1 and $x_1 + dx_1$ at maturity is therefore given by multiplying (3.1) and (3.2) and by then integrating with respect to x, that is

$$\frac{dx_1}{\sqrt{\pi}}\int_0^1 \sqrt{\frac{MN}{\pi x_0(1-x_0)}}\ \exp\left[-\frac{M(x-x_0)^2}{x_0(1-x_0)}-\frac{N(x_1-x)^2}{x(1-x)}\right]\frac{dx}{\sqrt{x(1-x)}} \quad . \qquad (3.3)$$

For $M >> N >> 1$,

$$\sqrt{\frac{M}{\pi x_0(1-x_0)}}\ \exp\left[-\frac{M(x-x_0)^2}{x_0(1-x_0)}\right] \cong \delta(x-x_0) \quad , \qquad (3.4)$$

the Dirac delta function, whence (3.3) is simply

$$\sqrt{\frac{N}{\pi x_0(1-x_0)}}\ \exp\left[-\frac{N(x_1-x_0)^2}{x_0(1-x_0)}\right]dx_1 \quad , \qquad (3.5)$$

the same as would have been obtained by going immediately from the N adults at $t = 0$ to the N surviving adults at $t = 1$, the adults who will give rise to the second generation at $t = 2$.

Likewise, the probability that the gene frequency at $t = 2$ lies between x_2 and $x_2 + dx_2$ is

$$\sqrt{\frac{N}{\pi x_1(1-x_1)}}\ \exp\left[-\frac{N(x_2-x_1)^2}{x_1(1-x_1)}\right] dx_2 \quad , \qquad (3.6)$$

when the frequency at $t = 1$ is taken as x_1. Combining (3.5) and (3.6), the total probability of the adults in the second generation having a frequency of the gene-type A lying between x_2 and $x_2 + dx_2$ is given by

$$dx_2\ \sqrt{\frac{N}{\pi x_0(1-x_0)}}\int_0^1 \sqrt{\frac{N}{\pi x_1(1-x_1)}}\ \cdot \exp\left[-\frac{N(x_1-x_0)^2}{x_0(1-x_0)} - \frac{N(x_2-x_1)^2}{x_1(1-x_1)}\right] dx_1 \quad . \qquad (3.7)$$

Since the population number N can be taken large, say $N = 10^6$, the exponentials in (3.7) give sharp peaks about x_0 and about x_1. Hence, so long as x_0 is not very close either to zero or unity, it is sufficiently accurate to replace $x_1(1 - x_1)$ by $x_0(1 - x_0)$, and also to expand the range of integration to $-\infty < x_1 < \infty$, giving

$$\sqrt{\frac{N}{2\pi x_0(1-x_0)}}\ \exp\left[-\frac{N(x_2-x_0)^2}{2x_0(1-x_0)}\right] dx_2 \quad . \qquad (3.8)$$

A similar argument going from $t = 2$ to the third generation at $t = 3$, and so on to the r'th generation at $t = r$ gives

$$\sqrt{\frac{N}{r\pi x_0(1-x_0)}}\ \exp\left[-\frac{N(x_r-x_0)^2}{rx_0(1-x_0)}\right] dx_r \qquad (3.9)$$

for the probability of the frequency of A lying between x_r and $x_r + dx_r$ after r generations. This is so long as the successive spreading of the exponentials from generation to generation does not lead to values of x_r with appreciable probability and such that $x_r(1 - x_r)$ is significantly different from $x_0(1 - x_0)$. When r becomes so large that this is not the case, the simple progression from generation to generation must cease, and a more complex procedure is then required. Before developing a formalism for such a procedure, let us return to what has so far been omitted—the effect of selection on the frequency of A.

Each generation has been considered to consist of two stages, a first stage from N mating adults to M juveniles, and then a second stage from the M juveniles to the N mating adults of the next generation. Although selection can enter both these stages, the second is usually the more important, and nothing of principle will be lost if we confine selection to it. The frequency of A among the juveniles being taken as x, the number of juveniles with A on both chromosome sets is Mx^2 to within a fluctuation that is only of small effect compared to the fluctuations already studied above. The number of heterozygotes with A on one chromosome set and a on the other is $2Mx(1 - x)$, and the number with a on both chromosome sets is $M(1 - x)^2$. Write $\alpha(1 + s)$ for the chance of an (A, A) juvenile surviving to reproduce the succeeding generation, write $\alpha(1 + hs)$ as the chance of a heterozygous juvenile, (A, a) or (a, A), surviving to maturity, and α for an (a, a) juvenile. Then α is determined by

$$\alpha M\left[(1+s)x^2 + 2(1+hx)x(1-x) + (1-x)^2\right] = N \quad . \qquad (3.10)$$

And the systematic change of the frequency x to $x + dx/dt$ in the parents of the next generation is given by

$$2N\left(x+\frac{dx}{dt}\right) = \alpha M\left[2(1+s)x^2+2(1+hs)x(1-x)\right] \quad . \qquad (3.11)$$

The right-hand side of equation (3.11) takes account of surviving heterozygotes having one chromosome set with A, each surviving (A, A) individual having two chromosome sets with A, and each surviving (a, a) individual being without A. From (3.10) and (3.11),

$$\frac{dx}{dt} = sx(1-x)\,\frac{[x+h(1-2x)]}{1+sx[x+2h(1-x)]} \quad . \qquad (3.12)$$

If $|s| << 1$, (3.12) can be written to sufficient accuracy as

$$\frac{dx}{dt} = sx(1-x)[x+h(1-2x)] \quad . \qquad (3.13)$$

In the special case $h = 1/2$, (3.13) takes the even simpler form

$$\frac{dx}{dt} = \frac{1}{2}sx(1-x) \quad . \qquad (3.14)$$

Except for the factor $1/2$, this is the same as the effect of selection in the asexual model of Chapter 1.

As well as the right-hand side of (3.13) being zero for $x = 0$ and $x = 1$, there is a third zero for

$$x = \frac{h}{2h-1} \quad . \qquad (3.15)$$

In order that (3.15) be a permissible value for the frequency of A, it is necessary that

$$0 \le \frac{h}{2h-1} \le 1 \quad , \qquad (3.16)$$

that is, $h \ge 1$ or $h \le 0$. To decide the stability or otherwise of the equilibrium value (3.15) in these cases, differentiate (3.13), the requirement for stability being

$$\left(\frac{d^2x}{dt^2}\right)_{x=h/2h-1} = -s\,\frac{h(h-1)}{2h-1} < 0 \quad , \qquad (3.17)$$

which is satisfied if either $s > 0$, $h > 1$ or $s < 0$, $h < 0$. Stable situations with $x = h/(2h-1)$ are known as balanced polymorphisms.

In studying a balanced polymorphism, it is really unnecessary to distinguish the two cases $s > 0$ and $s < 0$. The selective parameter was defined above by the condition that the ratio of the survival capabilities of juveniles of types (A, A) and (a, a) be $1 + s$, with the latter in the denominator when the ratio is taken. Equally, we could have written a as the surviving fraction of type (A, A) and $\alpha(1 + s)$ as the surviving fraction of type (a, a), when the ratio of survivors defining s would be inverted, with the sign of s reversed. Choosing the definition that leads to a specified sign of s, $s > 0$ say, determines the condition $h > 1$ for a balanced polymorphism to exist. The essential condition for a balanced polymorphism is that the heterozygotes, (A, a) or (a, A), must have a selective advantage over both homozygotes (A, A) and (a, a).

Stochastic fluctuations from generation to generation will cause the frequency x to be constantly shifting from the equilibrium value $h/(2h-1)$, but because the equilibrium is stable, the frequency always returns to this value, which is thus the complete solution to the behavior of A in such a case. Although I have heard expressions of opinion to the contrary from biologists, balanced polymorphisms are usually considered to be rare, and so I will consider them to be—otherwise there would be little more to do. From here on, therefore, I will suppose that A does not satisfy the condition for a

balanced polymorphism. Also from here on, I will make one or two minor changes of notation, as well as taking $|s|$ to be small compared to unity, in which case (3.13) is sufficiently accurate.

In the first generation the gene frequency changes due to selection from x_0 to $x_0 + y_0$, where from (3.13)

$$y_0 \cong sx_0(1-x_0)\left[x_0 + h(1-2x_0)\right] \quad . \tag{3.18}$$

In contrast to (3.18), which is a clear-cut increase or decrease in the frequency of A according to the sign of s, the stochastic fluctuation of the frequency, given by (3.5) for the first generation, may lead to either an increase or a decrease of frequency. Combining (3.5) and (3.18), the probability of the frequency of A lying between x_1 and $x_1 + dx_1$ after the first generation is given by

$$\sqrt{\frac{N}{\pi x_0(1-x_0)}}\ \exp\left[-\frac{N(x_1 - x_0 - y_0)^2}{x_0(1-x_0)}\right] dx_1 \quad . \tag{3.19}$$

And if x_0 is such that $x_1(1-x_1)$ is not appreciably different from $x_0(1-x_0)$, we can step along to the second generation, and so on to the r'th generation, provided $x_r(1-x_r)$ is not appreciably different from $x_0(1-x_0)$. Choosing r by this criterion, the probability that after r generations the frequency of A lies between x_r and $x_r + dx_r$ is given by

$$\sqrt{\frac{N}{r\pi x_0(1-x_0)}}\ \exp\left[-\frac{N(x_r - x_0 - ry_0)^2}{rx_0(1-x_0)}\right] dx_r \quad . \tag{3.20}$$

Instead of writing the times marking the generations by 0, 1, 2, ... , r, ... , with a trivial change of notation we can write $t_0, t_1, t_2, \ldots, t_r, \ldots$, with $t_r - t_{r-1} = 1$, when (3.20) takes the form

$$\sqrt{\frac{N}{\pi x_0(1-x_0)(t_r - t_0)}}\ \exp\left[-\frac{N(x_r - x_0 - y_0\overline{t_r - t_0})^2}{x_0(1-x_0)(t_r - t_0)}\right] \quad . \tag{3.21}$$

Defining a "propagator" by

$$k(x, t; x_0, t_0) = \sqrt{\frac{N}{\pi x_0(1-x_0)(t - t_0)}}\ \exp\left[-\frac{N(x - x_0 - y_0\overline{t - t_0})^2}{x_0(1-x_0)(t - t_0)}\right] \quad , \tag{3.22}$$

$k(x, t; x_0, t_0)$ is the probability to go from the frequency x_0 of gene-type A at time t_0 to the frequency x at time t, subject to the condition that $t - t_0$ must not be so large that $k(x, t; x_0, t_0)$ has appreciable values with $x(1-x)$ differing significantly from $x_0(1 - x_0)$. To give verbal assurance that the latter condition is satisfied let us refer to (3.22) as the "infinitesimal propagator."

Change the notation now so that $t_0, t_1, t_2, \ldots$ are times such that the infinitesimal propagator can be used sequentially, t_0 to t_1, t_1 to t_2, ... , the passage of time being thus broken up so that (3.22) can be used at each step. Note also that if instead of the gene frequency being specified uniquely at the initial moment t_0 we are given the more general boundary condition at t_0 that the gene frequency has the probability distribution $\phi(x_0, t_0)dx_0$, then the probability distribution $\phi(x_1, t_1)dx_1$ for the gene frequency at time t_1 is given by

$$\phi(x_1, t_1) = \int_0^1 k(x_1, t_1 ; x_0, t_0)\ \phi(x_0, t_0)\, dx_0 \quad . \tag{3.23}$$

For the next step from t_1 to t_2 we have in the same way

$$\phi(x_2, t_2) = \int_0^1 k(x_2, t_2 ; x_1, t_1)\ \phi(x_1, t_1)\, dx_1 \quad , \tag{3.24}$$

$k(x_2, t_2; x, t_1)$ being given by writing x_1, y_1, t_1 for x_0, y_0, t_0 and x_2, t_2 for x_1, t_1 in equation (3.22), with y_1 defined by

$$y_1 = sx_1(1-x_1)\left[x_1 + h(1-2x_1)\right] , \quad |s| << 1 . \tag{3.25}$$

Proceeding similarly step by step to time t_r,

$$\phi(x_r, t_r) = \int_0^1 \cdots \int_0^1 k(x_r, t_r; x_{r-1}, t_{r-1})\, k(x_{r-1}, t_{r-1}; x_{r-2}, t_{r-2}) \cdots k(x_1, t_1; x_0, t_0)\, \phi(x_0, t_0)\, dx_{r-1}\, dx_{r-2} \cdots dx_0 . \tag{3.26}$$

This result can be written compactly in terms of a finite propagator $K(x_r, t_r; x_0, t_0)$,

$$\phi(x_r, t_r) = \int_0^1 K(x_r, t_r; x_0, t_0)\, \phi(x_0, t_0)\, dx_0 , \tag{3.27}$$

where

$$K(x_r, t_r; x_0, t_0) = \int_0^1 \cdots \int_0^1 \left\{ \prod_{p=0}^{r-1} k(x_{p+1}, t_{p+1}; x_p, t_p) \right\} dx_{r-1} \cdots dx_1 , \tag{3.28}$$

with

$$k(x_{p+1}, t_{p+1}; x_p, t_p) = \sqrt{\frac{N}{\pi x_p(1-x_p)(t_{p+1}-t_p)}} \cdot \exp\left[- \frac{N\left(x_{p+1} - x_p - y_p\overline{t_{p+1}-t_p}\right)^2}{x_p(1-x_p)(t_{p+1}-t_p)} \right]$$

$$y_p = s\, x_p(1-x_p)\left[x_p + h(1-2x_p)\right] , \quad |s| << 1 . \tag{3.29}$$

The present formalism has analogy to problems in statistical mechanics in which repeated integrals like (3.26) are sometimes converted into a single-path integral, so that one can wonder if the present problem can be expressed as a path integral. With a suitable change of the variables it can.

Defining $\theta_0, \ldots, \theta_r$ by

$$\cos\theta_p = 1 - 2x_p, \quad p = 0, 1, \ldots, r , \tag{3.30}$$

the range of θ_p corresponding to $0 \le x_p \le 1$ is $0 \le \theta_p \le \pi$. After some reduction we then have

$$x_p(1-x_p) = \frac{1}{4}\sin^2\theta_p , \tag{3.31}$$

$$dx_p = \frac{1}{2}\sin\theta_p\, d\theta_p , \tag{3.32}$$

$$y_p = \frac{1}{8} s\, \sin^2\theta_p \left[1 + \cos\theta_p (2h-1)\right] , \tag{3.33}$$

and

$$\exp\left[- \frac{N\left(x_{p+1} - x_p - y_p\overline{t_{p+1} - t_p}\right)^2}{x_p\left(1-x_p\right)\left(t_{p+1} - t_p\right)}\right]$$

$$= \exp\left[- \frac{N\left(\cos\theta_p - \cos\theta_{p+1} - 2y_p\overline{t_{p+1} - t_p}\right)^2}{\sin^2\theta_p\left(t_{p+1} - t_p\right)}\right] \qquad (3.34)$$

It will be convenient to let the time-steps $t_{p+1} - t_p$ all be the same, ϵ say. Defining $\delta\theta_p$ by

$$\delta\theta_p = \theta_{p+1} - \theta_p \quad , \qquad (3.35)$$

and taking ϵ small enough for $\theta_{p+1} - \theta_p$ to be small,

$$\cos\theta_{p+1} \cong \cos\theta_p - \delta\theta_p \sin\theta_p \quad , \qquad (3.36)$$

whence (3.34) takes the more compact form

$$\exp\left[- N\epsilon\left(\frac{\delta\theta_p}{\epsilon} - \frac{2y_p}{\sin\theta_p}\right)^2\right] \quad . \qquad (3.37)$$

Lastly, defining

$$Q = \sqrt{\frac{\pi\epsilon}{N}} \quad , \qquad (3.38)$$

$$\mathcal{H}(p) = N\left(\frac{\delta\theta_p}{\epsilon} - \frac{2y_p}{\sin\theta_p}\right)^2$$

$$= N\left[\frac{\delta\theta_p}{\epsilon} - \frac{1}{4}s\,\sin\theta_p\left(1+\cos\theta_p\overline{2h-1}\right)\right]^2 \quad , \qquad (3.39)$$

Equation (3.28) can be expressed in the form

$$K(\theta_r, t_r\,;\theta_0, t_0) = \int_0^{\pi}\frac{d\theta_{r-1}}{Q}\cdots\int_0^{\pi}\frac{d\theta_1}{Q}\,\exp\left[-\epsilon\sum_{p=0}^{r-1}\mathcal{H}(p)\right] \qquad (3.40)$$

The function $\theta(t)$ can be thought of as a path going from θ_0 to θ_r by way of θ_1 at time t_1, θ_2 at time t_2, ..., θ_{r-1} at time t_{r-1}, with the path consisting of straight line segments between consecutive values of the time. In the (θ, t) plane start at θ_0, t_0 and go by a straight line segment to θ_1, t_1, then by a straight line segment to θ_2, t_2, and so on until θ_r, t_r is reached. The multiple integral (3.40) is a summation over all such functions $\theta(t)$. Moreover, for $\epsilon << 1$

$$\epsilon\sum_{p=0}^{r-1}\mathcal{H}(p) \cong N\int_{t_0}^{t_r}\left[\frac{d\theta}{dt} - \frac{1}{4}s\,\sin\theta\{1+\cos\theta(2h-1)\}\right]^2 dt \quad , \qquad (3.41)$$

the time integral being taken along $\theta(t)$ and so being a functional of $\theta(t)$. Using a notation introduced by Feynman (e.g., R. P. Feynman and A. R. Hibbs, *Quantum Mechanics and Path Integrals*, McGraw-Hill, 1965), (3.40) has the form

$$K(\theta_r,t_r\,;\theta_0,t_0)$$

$$= \int_{\theta_0}^{\theta_r} \exp\left[-N\int_{t_0}^{t_r}\left\{\frac{d\theta}{dt} - \frac{1}{4}s\,\sin\theta\left(1+\cos\theta\,\overline{2h-1}\right)\right\}^2 dt\right]\mathscr{D}\theta(t)\,. \tag{3.42}$$

Given that the gene frequency at t_0 is θ_0, the probability of the gene frequency being θ_r at t_r is therefore obtainable by a summation over all paths going from θ_0 to θ_r that satisfy the condition of being confined between $\theta = 0$ and $\theta = \pi$, with each path having a weight factor

$$\exp\left[-N\int_{t_0}^{t_r}\left\{\frac{d\theta}{dt} - \frac{1}{4}s\,\sin\theta\left(1+\cos\theta\,\overline{2h-1}\right)\right\}^2 dt\right] \quad . \tag{3.43}$$

In quantum mechanics, the problem of a particle in a potential field can be solved in a broadly similar way, with $K(x,\ t;\ x_0,\ t_0)$ being the wave function at time t for the case in which the particle is at x_0 at time t_0. If in quantum mechanics an experimental procedure were set up for determining where the particle happened to be at times intermediate between t_0 and t, we could say that the particle followed a certain explicit path. But in the absence of an experimental procedure the wave function $K(x,\ t;\ x_0,\ t_0)$ is necessarily obtained from a summation over paths, the procedure being similar to the above discussion of the gene problem. If in the latter we take a look at a particular population, in sufficient detail to determine the frequency of A at moments intermediate between t_0 and t, we can say by what explicit path the frequency went from its value at t_0 to its value at t. But if we do not look explicitly at the population it is impossible to say what particular path has been followed. Just as in quantum mechanics all we can do is to assign probabilities involving a summation over all paths.

There are two differences from quantum mechanics, however. In the latter a potential function enters the time integral in a factor analogous to

(3.43) only linearly, whereas the selection term in (3.43) is quadratic in s. Although second-order terms in s can usually be neglected for $s << 1$ with impunity, this is not so in (3.43) it may be noted. Except for small time differences $t_r - t_0$, the term in s^2 must be retained in attempting to evaluate the path integral (3.42). Also it may be noted that in quantum mechanics the index of the exponential in the path integral is purely imaginary instead of being real as in (3.42), a circumstance which is analogous to statistical mechanics, as was already said above.

But the big difference is that a particle confined in quantum mechanics to a coordinate range $0 \le x \le 1$ is usually regarded as being restricted by a box with perfectly reflecting walls, whereas in the gene problem paths which go to $x = 0$ or to $x = 1$ are not reflected, they stop. At $x = 0$, the gene-type A becomes extinct and cannot return, while at $x = 1$ the type A becomes possessed by every individual and the situation stays that way thereafter. Thus the gene problem is like a particle in a sticky box, with the particle adhering permanently should it touch the walls of the box.

The effect of extinction and of fixing in the gene problem is that

$$\int_0^1 K\left(x,t\,;x_0,t_0\right)dx \tag{3.44}$$

declines as t increases. Writing $P_{\text{ext}}(t)$ as the probability that by time t the gene-type A has become extinct, and denoting the probability that A has become fixed by $P_{\text{fix}}(t)$, conservation of probability gives

$$P_{\text{ext}}(t) + P_{\text{fix}}(t) + \int_0^1 K\left(x,t\,;x_0,t_0\right)dx = 1 \quad . \tag{3.45}$$

Moreover,

$$\frac{P_{\text{ext}}(t)}{P_{\text{fix}}(t)} = \frac{\displaystyle\int_{t_0}^{t} K\left(0,t\,;x_0,t_0\right)dt}{\displaystyle\int_{t_0}^{t} K\left(1,t\,;x_0,t_0\right)dt} \quad . \tag{3.46}$$

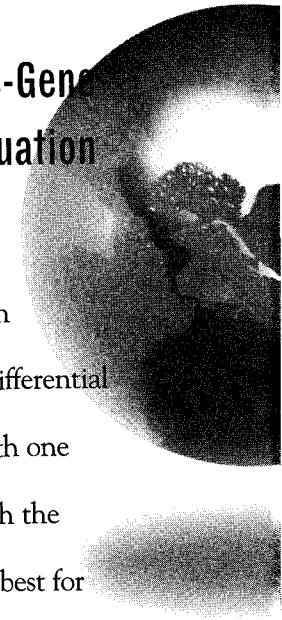
For any specified path the functional given by (3.43), $I[\theta(t)]$ say, can be evaluated. Then $K(\theta, t; \theta_0, t_0)$ can be obtained from

$$K(\theta,t;\theta_0,t_0) = \int_{\theta_0}^{\theta} I[\theta(t)]\,\mathcal{D}\theta(t) \qquad (3.47)$$

through quadratures performed at times intermediate between t_0 and t, remembering that the weight factor $Q = \sqrt{\pi \in/N}$ is needed, where $\in$ is the time-step employed. Since $K(\theta, t; \theta_0, t_0)$ with $x = (1 - \cos\theta)/2$ yields $K(x, t; x_0, t_0)$, three final quadratures in (3.45) to (3.47) determine $P_{ext}(t)$ and $P_{fix}(t)$, so completing the solution of the problem, since with adequate computing facilities numbers could actually be obtained. An alternative method of solution will be considered in the next chapter, which for the most part is not better than (3.47) but leads analytically to P_{ext}, P_{fix} in the limit $t \to \infty$.

Chapter 4

The Solution of the Single-Gene Problem by a Partial Differential Equation



Problems that can be dealt with by path integrals can also be studied by partial differential equations. Some issues are best dealt with one way while other issues are best dealt with the other way. The path integral method is best for short time intervals. Both methods are intractable in their full generality for long time intervals, although for restricted questions, solutions are sometimes determinable. Problems that can be

dealt with by path integrals can also be studied by partial differential equations. Some issues are best dealt with one way while other issues are best dealt with the other way. The path integral method is best for short time intervals. Both methods are intractable in their full generality for long time intervals, although for restricted questions, solutions are sometimes determinable. This is so in the present problem if instead of asking for a complete determination of the finite propagator $K(x, t; x_0, t_0)$ we ask for the cumulative probabilities over the entire time range $t_0 < t < \infty$ of the gene-type A becoming either fixed or extinct. It turns out that this particular problem can be solved by the partial differential equation method.

Since the work of Fisher in the 1920s it has been known that a partial differential equation for the fluctuation of A can be obtained in a manner analogous to the derivation of the thermal diffusion equation in physics, while the combination of fluctuations with selection yields a partial differential equation of the so-called Fokker-Planck type. I have not found it best, however, to follow these physical analogies, for the reason that one can all too easily be led into uncertainty over what quantities lie under differentiation signs. Indeed, Fisher himself fell a victim to this trouble in his early work and a similar mistake to Fisher's is to be found to this day in the equation used by astronomers for the diffusion of cometary orbits by the planet Jupiter, in my opinion.

The sovereign recipe for avoiding such troubles is to derive the required partial differential equation from the infinitesimal propagator by a method similar to that used for obtaining the Schrödinger equation in nonrelativistic quantum mechanics. From equation (3.24) the probablility distribution is obtained from an initially specified distribution $\phi(x', t')dx'$ for the frequency of the gene-type A by

$$\phi(x', t') = \int_0^1 K(x', t'; x_0, t_0)\, \phi(x_0, t_0)\, dx_0 \quad . \tag{4.1}$$

Here $\phi(x_0, t_0)$ is the initially specified probability function and K is the finite propagator, used when the time difference $t' - t_0$ is not too small. Consider a further *small* time-step from t' to t. Then

$$\phi(x, t) = \int_0^1 k(x, t; x', t')\, \phi(x', t')\, dx' \quad , \tag{4.2}$$

where $k(x, t; x', t')$ is the infinitesimal propagator given by

$$k(x, t; x', t') = \sqrt{\frac{N}{\pi x'(1-x')(t-t')}}\, \exp\left[-\frac{N(x - x' - y'\overline{t-t'})^2}{x'(1-x')(t-t')} \right] \quad , \tag{4.3}$$

$$y' = s x'(1-x') \frac{[x' + h(1-2x')]}{1 + s x'[x' + 2h(1-x')]} \quad . \tag{4.4}$$

Throughout this chapter, $|s|$ will be considered sufficiently small for (4.4) to be approximated as

$$y' = s x'(1-x')[x' + h(1-2x')] \quad . \tag{4.5}$$

The exponential in (4.3) is very sharp, because $N >> 1$ and $t - t'$ is a small time-step. Hence x must be close to x' if $k(x, t; x', t')$ is to be appreciably different from zero, and we can expand (4.5) by a Maclaurin series in terms of

$$y = s x(1-x)[x + h(1-2x)] \quad ,$$

that is,

$$y' = y + (x' - x)\frac{dy}{dx} + \frac{1}{2}(x' - x)^2 \frac{d^2 y}{dx^2} + \dots$$

$$= s x(1-x)[x + h(1-2x)] + s(x' - x)[\dots] + \dots \quad . \tag{4.6}$$

With $|x' - x|$ small, it is sufficiently accurate to omit all but the first two terms of (4.6). Now (4.2) can be rewritten as

$$\phi[x+y(t-t'),t]=\int_0^1 k\left(x+y\overline{t-t'},\,t\,;\,x',\,t'\right)\phi(x',t')\,dx' \quad , \tag{4.7}$$

by which device the first term on the right-hand side of (4.6) becomes transferred from the right to the left of (4.7), and expanding the left of (4.7) for $t - t'$ small we have

$$\phi(x,t')+(t-t')\left[y\frac{\partial\phi}{\partial x}+\frac{\partial\varphi}{\partial t}\right]_{t'}+\cdots$$

$$=\sqrt{\frac{N}{\pi}}\int_0^1 \exp\left[-\frac{N(x-x')^2\left(1+\overline{t-t'}\,\frac{dy}{dx}\right)^2}{x'(1-x')(t-t')}\right]\phi(x',t')\,\frac{dx'}{\sqrt{x'(1-x')(t-t')}} \quad . \tag{4.8}$$

It is sufficiently accurate to write

$$\exp\left[-\frac{N(x-x')^2\left(1+\overline{t-t'}\,\frac{dy}{dx}\right)^2}{x'(1-x')(t-t')}\right]$$

$$=\exp\left[-\frac{N(x-x')^2\left(1+2\overline{t-t'}\,\frac{dy}{dx}\right)}{x'(1-x')(t-t')}\right]$$

$$=\exp\left[-\frac{N(x-x')^2}{x'(1-x')(t-t')}\right]\left[1-\frac{2N(x-x')^2\,\frac{dy}{dx}}{x'(1-x')}+\cdots\right] \tag{4.9}$$

To obtain the required partial differential equation, we have to insert (4.9) in (4.8) and then evaluate the resulting integral with respect to x'.

Facing this task as best one can, put

$$z=\frac{x'-x}{\sqrt{x'(1-x')}} \quad , \tag{4.10}$$

changing the variable of integration from x' to z. Because of the sharpness of the exponential in (4.9), it is sufficient to evaluate the other terms in the integral (4.8) with $|z|$ small, that is, in ascending powers of z. Thus

$$\frac{dx'}{\sqrt{x'(1-x')}}=\left[1+\frac{1-2x}{2\sqrt{x(1-x)}}\,z-z^2+0\left(z^3\right)\right]dz \quad , \tag{4.11}$$

$$x'-x=\sqrt{x(1-x)}\,z+\tfrac{1}{2}(1-2x)\,z^2+0\left(z^3\right) \quad . \tag{4.12}$$

And expanding $\phi(x', t')$ about $x' = x$,

$$\phi(x',t')=\phi(x,t')+(x'-x)\frac{\partial\phi(x,t')}{\partial x}+\frac{1}{2}(x'-x)^2\frac{\partial^2\phi(x,t')}{\partial x^2}+\cdots \tag{4.13}$$

Inserting (4.12),

$$\phi(x',t')=\phi(x,t')+\sqrt{x(1-x)}\,z\frac{\partial\varphi}{\partial x}$$

$$+\frac{1}{2}z^2\left[(1-2x)\frac{\partial\varphi}{\partial x}+x(1-x)\frac{\partial^2\varphi}{\partial x^2}\right]+\cdots \tag{4.14}$$

Hence, to terms of order z^2, the right-hand side of (4.8) is

$$\sqrt{\frac{N}{\pi(t-t')}}\int_{-\infty}^{\infty}\exp\left[-\frac{Nz^2}{t-t'}\right]\cdot\left[1-2N\frac{dy}{dx}z^2\right]\cdot\left[1+\frac{1-2x}{2\sqrt{x(1-x)}}z-z^2\right]$$
$$\cdot\left[\phi(x,t')+\sqrt{x(1-x)}\,z\frac{\partial\varphi}{\partial x}+\frac{1}{2}z^2\left\{(1-2x)\frac{\partial\varphi}{\partial\phi}+x(1-x)\frac{\partial^2\varphi}{\partial x^2}\right\}\right]dz \tag{4.15}$$

the range $0 \le x' \le 1$ yielding the range from $-\infty$ to ∞ for z. All the z-dependent terms in (4.15) can be evaluated up to order z^2 by using

$$\int_{-\infty}^{\infty}\exp\left[-\frac{Nz^2}{t-t'}\right]dz=\sqrt{\frac{\pi(t-t')}{N}}\quad, \tag{4.16}$$

$$\int_{-\infty}^{\infty}\exp\left[-\frac{Nz^2}{t-t'}\right]z\,dz=0\quad, \tag{4.17}$$

$$\int_{-\infty}^{\infty}\exp\left[-\frac{Nz^2}{t-t'}\right]z^2dz=\frac{1}{2}\sqrt{\pi}\left(\frac{t-t'}{N}\right)^{3/2}\quad. \tag{4.18}$$

Thus the right-hand side of (4.8) is

$$\left[1-(t-t')\frac{dy}{dx}\right]\phi(x,t')$$
$$+\frac{1}{2}\frac{(t-t')}{N}\left[-\phi(x,t')+(1-2x)\frac{\partial\varphi}{\partial x}+\frac{1}{2}x(1-x)\frac{\partial^2\varphi}{\partial x^2}\right]\quad. \tag{4.19}$$

Hence the required partial differential equation is

$$\frac{\partial\varphi}{\partial t}+\frac{\partial}{\partial x}(y\phi)=\frac{1}{2N}\left[\frac{1}{2}x(1-x)\frac{\partial^2\varphi}{\partial x^2}+(1-2x)\frac{\partial\varphi}{\partial x}-\varphi\right]$$
$$=\frac{1}{4N}\frac{\partial^2}{\partial x}[x(1-x)\varphi]\quad. \tag{4.20}$$

Let us consider, first, the case where A is a neutral mutation, that is, $s = 0$, $y = 0$. The separable form

$$\phi(x,t)=F(x)\,\exp\left[-\frac{w^2}{4N}(t-t_0)\right] \tag{4.21}$$

is then a solution if $F(x)$ satisfies the ordinary differential equation

$$x(1-x)\frac{d^2F}{dx^2}+2(1-2x)\frac{dF}{dx}+\left(w^2-2\right)F=0\quad. \tag{4.22}$$

For w^2 real, (4.22) has the form of the hypergeometric equation, which in canonical form is

$$x(1-x)\frac{d^2F}{dx^2}+[c-(a+b+1)x]\frac{dF}{dx}-abF=0\quad. \tag{4.23}$$

The solution $F(a, b; c; x)$ of (4.23) equal to unity at $x = 0$ has the series form

$$F(a,b;c;x)=1+\frac{a\cdot b}{1\cdot c}x+\frac{a(a+1)b(b+1)}{1\cdot2\cdot c(c+1)x^2}$$
$$+\frac{a(a+1)(a+2)\cdot b(b+1)(b+2)}{1\cdot2\cdot3\cdot c(c+1)(c+2)}x^3+\ldots \tag{4.24}$$

Identifying coefficients between (4.22) and (4.23) and noting that $F(a, b; c; x) = F(b, a; c; x)$,

$$a = \frac{3}{2} - \sqrt{w^2 + \frac{1}{4}} \quad , \quad b = \frac{3}{2} + \sqrt{w^2 + \frac{1}{4}} \quad , \quad c = 2 \qquad (4.25)$$

determines the solution of (4.20) subject to $\varphi(x, t)$ having the separable form (4.21).

When w^2 is a member of the sequence $n(n + 1)$, $n = 1, 2, \ldots$, the solution takes the form $F(1 - n, 2 + n; 2; x)$ for which the series (4.24) can be seen to terminate. The series becomes a polynomial in x of degree x^{n-1}. The essential point of the above analysis now emerges, for the polynomials $F(1 - n, 2 + n; 2; x)$, $n = 1, 2, \ldots$, are a *complete* set. Hence the most general solution of (4.20) can be expanded in terms of them,

$$\phi(x, t) = \sum_{n=1}^{\infty} \beta_n \, F(1-n, 2+n; 2; x) \exp\left[- \frac{n(n+1)(t-t_0)}{4N} \right] \quad , \qquad (4.26)$$

where β_n, $n = 1, 2, \ldots$ are constants to be determined from the initially specified form of φ, $\varphi(x, t_0)$. If, for example, the gene frequency has a uniquely specified value x_0 at time t_0,

$$\varphi(x, t_0) = \delta(x - x_0) \quad , \qquad (4.27)$$

where $\delta(x - x_0)$ is the Dirac delta function and the β_n are to be obtained from

$$\sum_{n=1}^{\infty} \beta_n \, F(1-n, 2+n; 2; x) = \delta(x - x_0) \quad . \qquad (4.28)$$

The polynomials $F(1 - n, 2 + n; 2; x)$ have the further useful property of being orthogonal with respect to $x(1 - x)$ as weight factor,

$$\int_0^1 F(1-m, 2+m; 2; x) F(1-n, 2+n; 2; x) \, x(1-x) \, dx$$

$$= \frac{1}{n(n+1)(2n+1)} \qquad \text{if } m = n$$

$$= 0 \qquad \text{if } m \neq n \quad . \qquad (4.29)$$

To determine β_n in the case (4.27) multiply (4.28) by $x(1 - x)$ $F(1 - m, 2 + m; 2; x)$ and integrate with respect to x from 0 to 1. All terms give zero on the left except $n = m$ because of (4.29) and

$$\frac{\beta_m}{m(m+1)(2m+1)} = \int_0^1 x(1-x) \, F(1-m, 2+m; 2; x) \, \delta(x - x_0) \, dx$$

$$= x_0(1 - x_0) \, F(1-m, 2+m; 2; x_0) \, , \quad m = 1, 2, \ldots \qquad (4.30)$$

Substituting for the coefficients β from (4.30) into (4.26) solves the problem of the behavior of a neutral mutation having a definite frequency x_0 at $t = t_0$. Thus the finite propagator $K(x, t; x_0, t_0)$ is given in the neutral case by

$$K(x, t; x_0, t_0) = \sum_{n=1}^{\infty} x_0(1 - x_0) \, n(n+1)(2n+1) \, F(1-n, 2+n; 2; x_0)$$

$$\bullet \; F(1-n, 2+n; 2; x) \exp\left[- \frac{n(n+1)(t-t_0)}{4N} \right] \quad , \qquad (4.31)$$

a result stated by Kimura in his book *The Neutral Theory of Molecular Evolution* (Cambridge, 1984).

For consistency, (4.31) must tend to the infinitesimal propagator as $t \to t_0$. When $s = 0$, $y = 0$, the latter is

$$k(x, t\,;\, x_0, t_0) = \sqrt{\frac{N}{\pi x_0(1-x_0)(t-t_0)}}\ \exp\left[-\frac{N(x-x_0)^2}{x_0(1-x_0)(t-t_0)}\right] . \tag{4.32}$$

Possibly there is some elegant way to show that as $t \to t_0$

$$x_0(1-x_0)\sum_{n=1}^{\infty} n(n+1)(2n+1)\,F(1-n, 2+n\,;2;\,x_0)\,\bullet$$

$$F(1-n,\,2+n;\,2;\,x)\,\exp\left[-\frac{n(n+1)(t-t_0)}{4N}\right]$$

$$\to \sqrt{\frac{N}{\pi x_0(1-x_0)(t-t_0)}}\ \exp\left[-\frac{N(x-x_0)^2}{x_0(1-x_0)(t-t_0)}\right] , \tag{4.33}$$

but if so, I have not been able to find it. I will spare the reader the acute misery I encountered in trying to prove (4.33), giving only a sketch of my calculation, which did indeed arrive at its goal in the bitter end. The trouble is that the series on the left-hand side of (4.33) is dominated at small $t - t_0$ by many terms at large values of n. One must start therefore, it seemed to me, by finding an asymptotic form for the hypergeometric polynomials. Those mathematical vade mecums with which modern publishers seek to ease the life of the younger generation proved to be silent on this matter. However, there are relations between the hypergeometric polynomials and other systems of orthogonal polynomials, in particular

$$F(1-n,\,2+n\,;\,2;\,x) = \frac{2}{n(n+1)}\,\frac{d}{d(1-2x)}\left[P_n(1-2x)\right] , \tag{4.34}$$

where $P_n(1 - 2x)$ is the Legendre polynomial $P_n(\cos\theta)$ with $\cos\theta = 1 - 2x$. A toehold could then be gained from a known asymptotic form for the Legendre polynomials,

$$P_n(\cos\theta) \doteq \sqrt{\frac{2}{\pi n \sin\theta}}\,\sin\left[(n+\tfrac{1}{2})\theta + \frac{\pi}{4}\right] . \tag{4.35}$$

Now put (4.35) in (4.34) and substitute the resulting expressions for $F(1 - n, 2 + n; 2; x)$ and $F(1 - n, 2 + n; 2; x_0)$ in (4.33), and then proceed to the not-so-exquisite problem of summing the resulting series. The outcome, after an unattractive trigonometrical reduction followed by replacing the series by an integral, was indeed the right-hand side of (4.33), which at least convinced me that in mathematics there is justice, if rough, and this is more than you can say for most of the other activities of humankind.

This experience made me wonder just how useful the result (4.31) really is. It is the convention in mathematics for any problem that can be expressed in terms of known functions like the hypergeometric functions to be regarded as solved. As long as a procedure can be specified whereby any question about the problem one cares to ask could in principle be answered, the problem is "solved," regardless of whether in practice the procedure really could be carried out. Some logicians have questioned such a style of argument, especially where critical mathematical proofs are concerned, as for instance where the so-called axiom of choice is concerned. My own view of this old controversy is that one has to distinguish sharply between procedures that really could be pushed through if sufficient trouble were taken by a sufficient number of people, and imagined procedures which really could not be carried out no matter how much human effort were expended. The latter I would regard as dubious, the former as permissible. There is no doubt that the present problem of determining $K(x, t; x_0, t_0)$ falls into the permissible class. Given x_0, t_0, numerical values for $K(x, t; x_0, t_0)$ at specified x, t could in practice be found if one were sufficiently determined about it. How determined would one have to be?

The saving grace of the solution (4.31) is that the exponential factors $\exp[-n(n+1)(t-t_0)/4N]$ produce rapid convergence for time differences $t-t_0$ of order N. Moreover, the series expansions for $F(1-n, 2+n; 2; x)$ and for $F(1-n, 2+n; 2; x_0)$ terminate quickly for low values of n. Thus for large time differences (4.31) could be made to yield explicit numbers for the finite propagator $K(x, t; x_0, t_0)$. On the other hand, for small time differences the series expansion (4.31) is impractical for the reasons already discussed above—the convergence is atrociously slow. But for small time differences we have the path integral method discussed in the previous chapter. Indeed, for $t-t_0$ small enough we already have a simple formula for the propagator, the infinitesimal propagator

$$K(x, t; x_0, t_0) = k(x, t; x_0, t_0) = \sqrt{\frac{N}{\pi x_0(1-x_0)(t-t_0)}}\exp\left[-\frac{N(x-x_0-y_0\overline{t-t_0})^2}{x_0(1-x_0)(t-t_0)}\right] . \tag{4.36}$$

As $t-t_0$ increases it becomes necessary to have more and more steps in the path integral, which is the way r increases in the expression

$$K(x_r, t_r; x_0, t_0) = \int_0^1 \cdots \int_0^1 \prod_{p=o}^{r-1} k(x_{p+1}, t_{p+1}; x_p, t_p)\, dx_1 \cdots dx_{r-1}$$

$$k(x_{p+1}, t_{p+1}; x_p, t_p) = \sqrt{\frac{N}{\pi x_p(1-x_p)(t_{p+1}-t_p)}}\exp\left[-\frac{N(x_{p+1}-x_p-y_p\overline{t_{p+1}-t_p})^2}{x_p(1-x_p)(t_{p+1}-t_p)}\right]$$

$$y_p = s x_p(1-x_p)\left[x_p + h(1-2x_p)\right], \qquad |s| \ll 1 . \tag{4.37}$$

For $t_r - t_0$ of order N it would typically be necessary to perform about a hundred quadratures in order to obtain $K(x_r, t_r; x_0, t_0)$ for specified x_r, t_r. With a modern high-speed computer such a computation would not be out of the question, but of course the series expansion (4.31) is much preferable to the path integral for large $t-t_0$. *This is provided the selection factor* s *is zero,* provided the mutation under discussion is neutral. When $s \neq 0$ the arithmetical labour of using the path integral method is scarcely affected, whereas attempts to obtain a series expansion similar to (4.31) appear doomed to failure. With the $\partial(y\phi)/\partial x$ term in (4.20) included, my attempts to find a general solution failed. Nor could I find anything useful in well-known books on special functions. Yet remarkably enough, although (4.20) was not helpful for the general purpose of determining $K(x, t; x_0, t_0)$ analytically, the partial differential equation provides the solution to a problem, which although limited in scope, is nevertheless important. This is the problem of determining the cumulative probability of the gene A becoming fixed ($x = 1$) and of it becoming extinct ($x = 0$), cumulative over the whole time interval from $x = x_0$ at $t = t_0$ to $t \to \infty$.

Writing out (4.20) in full,

$$\frac{\partial \varphi}{\partial t} = \frac{1}{4N}\frac{\partial^2}{\partial x^2}\left[x(1-x)\phi\right] - s\frac{\partial}{\partial x}\left[x(1-x)\{x+h(1-2x)\}\phi\right] , \tag{4.38}$$

whence

$$\frac{\partial}{\partial t}\int_0^1 \phi\, dx = \frac{1}{4N}\left[\frac{\partial}{\partial x}\{x(1-x)\phi\} - s\,x(1-x)\{x+h(1-2x)\}\,\phi\right]_0^1$$

$$= -\frac{1}{4N}\{\phi(x=0,t) + \phi(x=1,t)\} . \tag{4.39}$$

The left-hand side of (4.39) is the rate of increase of the total probability of the gene frequency lying between 0 and 1. The increase being negative, the probability of the gene frequency lying in the open interval (0, 1) decreases, and it does so through what can be called an outflow of probability, an outflow at $x = 0$ representing the probability per unit time that the gene

becomes extinct, and an outflow at $x = 1$ representing the probability per unit time that the gene becomes fixed. These are the two terms on the right-hand side of (4.39). The cumulative probability of fixing A is therefore

$$\frac{1}{4N}\int_{t_0}^{\infty}\phi\,(x=1,\ t)\,dt = P_{\text{fix}} \quad \text{say,} \tag{4.42}$$

and the cumulative probability of A becoming extinct is, say,

$$\frac{1}{4N}\int_{t_0}^{\infty}\phi\,(x=0,\ t)\,dt = P_{\text{ext}} \quad \text{say} \quad . \tag{4.43}$$

Although the partial differential equation (4.38) is intractable for determining $K(x, t; x_0, t_0)$ when $s \neq 0$, it turns out that the less ambitious problem of determining P_{fix} and P_{ext} can indeed be solved.

Provided the special and unusual cases of balanced polymorphisms that were mentioned in Chapter 3 are excluded, the gene-type A eventually becomes either extinct or fixed, so that

$$P_{\text{ext}} + P_{\text{fix}} = 1 \quad . \tag{4.44}$$

That is to say,

$$\phi\,(x, t) \to 0 \quad , \quad t \to \infty \tag{4.45}$$

for all x in the open interval (0, 1). Note also that $\phi(x = 0, t)$ and $\phi(x = 1, t)$ in (4.41) are defined by continuity from (0, 1) to its end points, a situation that is common for partial differential equations (c.f., *Methods of Mathematical Physics*, section 10, page 324, R. Courant and D. Hilbert, New York: Interscience, 1953). Hence at any x in (0, 1) we have

$$\int_{t_0}^{\infty}\frac{\partial\phi(x,t)}{\partial t}\,dt = -\phi\,(x, t_0) = -\delta\,(x - x_0) \quad , \tag{4.46}$$

it being supposed that at time t_0 the gene frequency is known to be x_0, as for example $x_0 = 1/2N$ when a mutation occurs. From (4.38) we have

$$\int_{t_0}^{\infty}\frac{\partial\phi(x,t)}{\partial t}dt = \frac{1}{4N}\frac{d^2}{dx^2}\left[x(1-x)\int_{t_0}^{\infty}\phi\,(x,t)dt\right] - s\frac{d}{dx}\left[x(1-x)\{x+h(1-2x)\}\int_{t_0}^{\infty}\phi\,(x,t)dt\right] . \tag{4.47}$$

Defining

$$\mu\,(x) = \int_{t_0}^{\infty}\phi\,(x,\ t)\,dt \tag{4.48}$$

we therefore have

$$-\delta\,(x - x_0) = \frac{1}{4N}\frac{d^2}{dx^2}[x(1-x)\mu] - s\frac{d}{dx}[x(1-x)\{x+h(1-2x)\}\mu] \quad . \tag{4.49}$$

Comparing (4.42), (4.43), and (4.48), we see that

$$P_{\text{fix}} = \frac{1}{4N}\mu\,(x=1) \quad , \quad P_{\text{ext}} = \frac{1}{4N}\mu\,(x=0) \quad . \tag{4.50}$$

Hence the problem of obtaining P_{fix} and P_{ext} reduces to the problem of solving the ordinary differential equation (4.49).

Except at $x = x_0$, the left-hand side of (4.49) is zero, and the equation with zero on the left-hand side has an immediate first integral

$$\frac{d}{dx}[x(1-x)\mu] - 4Nsx(1-x)[x+h(1-2x)]\mu = \text{Constant}. \qquad (4.51)$$

A solution for $\mu(x)$ satisfying (4.51) holds in both the open intervals $(0, x_0)$ and $(x_0, 1)$, but with different constants on the right-hand side, because of the delta function in (4.49) which requires $d\mu/dx$ to be a step function across $x = x_0$. On the other hand, $\mu(x)$ is continuous across $x = x_0$. Let C be the constant for $(0, x_0)$ and C' the constant for $(x_0, 1)$. The equation

$$\frac{d}{dx}[x(1-x)\mu] - 4Nsx(1-x)[x+h(1-2x)]\mu = C \qquad (4.52)$$

for $(0, x_0)$ has $\exp[-2Ns\{x^2 + 2h(x - x^2)\}]$ as an integrating factor, whence

$$x(1-x)\exp\left[-2Ns\left\{x^2+2h\left(x-x^2\right)\right\}\right]\mu(x)$$

$$= C\int_0^x \exp\left[-2Ns\left\{z^2+2h\left(z-z^2\right)\right\}\right]dz$$

$$= Cf(x, 0) \quad \text{say}, \quad 0 \le x < x_0 \quad . \qquad (4.53)$$

Similarly,

$$x(1-x)\exp\left[-2Ns\left\{x^2+2h\left(x-x^2\right)\right\}\right]\mu(x)$$

$$= C'\int_x^1 \exp\left[-2Ns\left\{z^2+2h\left(z-z^2\right)\right\}\right]dz$$

$$= C'f(1, x) \quad \text{say}, \quad x_0 < x \le 1 \quad . \qquad (4.54)$$

Continuing $\mu(x)$ at $x = x_0$ requires

$$Cf\left(x_0, 0\right) = C' f\left(1, x_0\right) \quad . \qquad (4.55)$$

Integration of (4.49) from $x_0 - \epsilon$ to $x_0 + \epsilon$ for $\epsilon << 1$ also gives

$$\frac{1}{4N}x_0\left(1-x_0\right)\left[\left(\frac{d\mu}{dx}\right)_{x=x_0+\epsilon} - \left(\frac{d\mu}{dx}\right)_{x=x_0-\epsilon}\right] = -1 \quad , \qquad (4.56)$$

which from (4.53) and (4.54) requires C and C' to satisfy

$$C + C' = 4N \quad . \qquad (4.57)$$

From (4.55) and (4.57),

$$C = \frac{4N}{1+f\left(x_0, 0\right)/f\left(1, x_0\right)} \quad , \qquad C' = \frac{4N}{1+f\left(1, x_0\right)/f\left(x_0, 0\right)} \quad . \qquad (4.58)$$

Now from (4.53)

$$\mu(x) \to C \qquad \text{as} \quad x \to 0 \quad , \qquad (4.59)$$

and from (4.54)

$$\mu(x) \to C' \qquad \text{as} \quad x \to 1 \quad . \tag{4.60}$$

From (4.50), (4.58), (4.59), and (4.60), the required probabilities P_{fix} and P_{ext} are determined by

$$P_{\text{fix}} = \frac{f(x_0,0)}{f(x_0,0)+f(1,x_0)} \quad , \tag{4.61}$$

$$P_{\text{ext}} = \frac{f(1,x_0)}{f(x_0,0)+f(1,x_0)} \quad , \tag{4.62}$$

where

$$f(x_0,0) = \int_0^{x_0} \exp\left[-2Ns\left\{x^2+2h\left(x-x^2\right)\right\}\right]dx \quad , \tag{4.63}$$

$$f(1,x_0) = \int_{x_0}^{1} \exp\left[-2Ns\left\{x^2+2h\left(x-x^2\right)\right\}\right]dx \quad . \tag{4.64}$$

All that remains of our problem is to evaluate (4.63) and (4.64) for various choices of s and h. As far as the selection factor s is concerned, we are interested in both $s > 0$ and $s < 0$, and in both $2N|s| << 1$ and $2N|s| >> 1$.

The case $2N|s| << 1$ is easily dealt with. This is the case of an effectively neutral mutation, with $f(x_0, 0) \cong x_0 = 1/2N$ and $f(1, x_0) \cong 1 - x_0 = 1 - 1/2N$. From (4.61), (4.62)

$$P_{\text{fix}} \cong f(x_0, 0) = \frac{1}{2N}$$

$$P_{\text{ext}} = 1 - P_{\text{fix}} \cong 1 - \frac{1}{2N} \quad , \tag{4.65}$$

which are well-known results also derivable, awkwardly in my experience, from the series (4.31) and more easily by an argument given by the writer together with Professor Chandra Wickramasinghe in the lecture note reprint *Why Neo-Darwinism Does Not Work* (University College Cardiff Press, 1982).

The integrals (4.63) and (4.64) can be evaluated immediately for the case $h = 1/2$, which is to say,

$$f(x_0,0) = \int_0^{x_0} \exp(-2Nsz)\,dz = \frac{1}{2Ns}\left[1-\exp\left(-2Nsx_0\right)\right] \quad ,$$

$$f(1,x_0) = \int_{x_0}^{1} \exp(-2Nsz)\,dz = \frac{1}{2Ns}\left[\exp\left(-2Nsx_0\right)-\exp(-2Ns)\right] \quad , \tag{4.66}$$

giving

$$P_{\text{fix}} = \frac{1-\exp\left(-2Nsx_0\right)}{1-\exp(-2Ns)} \quad , \tag{4.67}$$

$$P_{\text{ext}} = \frac{\exp\left(-2Nsx_0\right)-\exp(-2Ns)}{1-\exp(-2Ns)} \quad . \tag{4.68}$$

For $2N|s| >> 1$, an advantageous mutation with $s > 0$, $x_0 = 1/2N$, gives

$$P_{\text{fix}} \cong 1 - \exp(-s) \cong s \quad ,$$

$$P_{\text{ext}} = \exp(-s) \cong 1 - s \quad , \quad s << 1 \quad . \tag{4.69}$$

For $s < 0$, on the other hand,

$$P_{\text{fix}} \cong |s| \exp(-2N|s|) \cong 0$$

$$P_{\text{ext}} = 1 - P_{\text{fix}} \cong 1 \quad . \tag{4.70}$$

The theory only does in part what according to neo-Darwinian concepts it is supposed to do—deleterious mutations with $2N|s| >> 1$ are prevented from becoming fixed. But the theory does not add up "all that is good," it adds only a fraction s of advantageous mutations, so that for $0 < s << 1$ the fraction is small.

The situation for other values of the parameter h is qualitatively the same. In all cases with $x_0 = 1/2N << 1$, $2N|s| >> 1$, $|s| << 1$, we have

$$2N|s|\left[x^2 + 2h\left(x - x^2\right)\right] << 1 \qquad \text{for } x \le x_0 \quad , \tag{4.71}$$

so that

$$f(x_0, 0) = \int_0^{x_0} \exp\left[-2Ns\left\{x^2 + 2h\left(x - x^2\right)\right\}\right] dx \cong x_0 = \frac{1}{2N} \quad , \tag{4.72}$$

$$f(1, x_0) = \int_{x_0}^{1} \exp\left[-2Ns\left\{x^2 + 2h\left(x - x^2\right)\right\}\right] dx$$

$$\cong \int_0^1 \exp\left[-2Ns\left\{x^2 + 2h\left(x - x^2\right)\right\}\right] dx >> f(0, x_0) \tag{4.73}$$

Hence

$$P_{\text{fix}} = \frac{1}{1 + f(1, x_0)/f(x_0, 0)} \cong \frac{f(x_0, 0)}{f(1, x_0)} \cong \frac{1}{2N f(1, 0)} \quad , \tag{4.74}$$

and the situation reduces to the evaluation of

$$f(1, 0) = \int_0^1 \exp\left[-2Ns\left\{x^2 + 2h\left(x - x^2\right)\right\}\right] dx \quad , \tag{4.75}$$

since of course $P_{\text{ext}} = 1 - P_{\text{fix}}$ is obtained immediately and P_{fix} is determined.

For the case $h = 0$, $s > 0$, $2Ns >> 1$,

$$f(1,0) = \int_0^1 \exp\left(-2Nsx^2\right) dx \cong \int_0^\infty \exp\left(-2Nsx^2\right) dx = \sqrt{\frac{\pi}{8Ns}} \tag{4.76}$$

For the case $h = 0$, $s < 0$, $2N|s| >> 1$,

$$f(1,0) = \int_0^1 \exp\left(2N|s|x^2\right) dx$$

$$\cong \int_0^1 \exp\left(2N|s|x^2\right) x\, dx \cong \frac{1}{4N|s|} \exp(2N|s|) \quad . \tag{4.77}$$

For the case $h = 1$, $s > 0$, $2Ns >> 1$,

$$f(1,0) = \int_0^1 \exp\left[2Ns\left(x^2 - 2x\right)\right] dx$$

$$= \exp(-2Ns) \int_0^1 \exp\left[2Ns(x-1)^2\right] dx$$

$$= \exp(-2Ns) \int_0^1 \exp\left[2Nsz^2\right] dz$$

$$\cong \exp(-2Ns) \int_0^1 \exp\left[2Nsz^2\right] z\, dz \cong \frac{1}{4Ns} \tag{4.78}$$

For the case $h = 1$, $s < 0$, $2N|s| >> 1$,

$$f(1,0) = \exp(2N|s|)\int_0^1 \exp\left(-2N|s|z^2\right)dz$$

$$\cong \exp(2N|s|)\int_0^\infty \exp\left(-2N|s|z^2\right)dz$$

$$= \sqrt{\frac{\pi}{8N|s|}}\exp(2N|s|) \quad . \tag{4.79}$$

Inserting (4.76) to (4.79) in (4.74) gives P_{fix} for the respective cases, which it will be useful to collect into a table by way of completing the present chapter.

Table 4.1 *Probabilities of Fixing and of the Extinction of a Mutant Gene ($2N|s| >> 1$)*

Case	P_{fix}	P_{ext}
$h=0,\quad s>0$	$\sqrt{2s/\pi N}$	$1-\sqrt{2s/\pi N}$
$h=0,\quad s<0$	$2\lvert s\rvert \exp(-2N\lvert s\rvert)$	$1-2\lvert s\rvert \exp(-2N\lvert s\rvert)$
$h=\frac{1}{2},\quad s>0$	s	$1-s$
$h=\frac{1}{2},\quad s<0$	$\lvert s\rvert\exp(-2N\lvert s\rvert)$	$1-\lvert s\rvert\ \exp(-2N\lvert s\rvert)$
$h=1,\quad s>0$	$2s$	$1-2s$
$h=1,\quad s<0$	$\sqrt{2\lvert s\rvert/\pi N}\exp(-2N\lvert s\rvert)$	$1-\sqrt{2\lvert s\rvert/\pi N}\ \exp(-2N\lvert s\rvert)$

Cases of balanced polymorphisms in which a gene neither fixes nor becomes extinct are excluded here. From Chapter 3, these are cases with $s > 0$, $h > 1$, or alternatively, $s < 0$, $h < 0$.

Chapter 5

Sociological Consequences of Deleterious Mutation Pressure

Deleterious mutations with $|s| << 1$ were shown in the single parent-to-offspring of Chapter 1 to have two unwelcome consequences, both of which also arise in the sexual model studied in the last three chapters. One is that the fitness is reduced by a factor $\exp -\lambda$ for a whole species below that of an initially homogeneous population, where λ is the average number of mutations occurring per

individual per generation. The other is to produce a slow erosion of a species from the initial standard of reference, at a rate that is dependent on the population N. For $N > 10^6$ the rate is slower than in the single parent-to-offspring model, but for small populations, erosion is critical. In the first part of this chapter I will establish these results mathematically, and then in the second half I will discuss certain of their consequences explicitly for human populations.

A major fraction of deleterious mutations involve the cancellation of a positive property of some gene rather than in causing some entirely new property of devastating consequence to arise. The protein to which the mutated gene gives expression becomes a dud; it sits around doing nothing useful instead of actively fulfilling it proper function. In such a situation there will be no bad effect provided the dud protein is shouldered aside, and so long as the corresponding gene on the alternative set of chromosomes is in working order, and provided the supply of the correct protein from the working gene is as much as is needed. For such a deleterious mutation A, the heterozygotes in the population possessing only one A feel no ill effect from it, because the bad A is shielded by the good *a*. It is only the unfortunate members of the population who happen to have A on both chromosome sets that feel its ill effect. Such a situation is represented by the case $s < 0$, $h = 0$, which I consider first. We can contemplate that $|s|$ in such a situation might be quite large, even of order unity, because if an essential protein were knocked out on both chromosome sets, the consequences could be seriously debilitating, perhaps even lethal. Since the analysis to this stage has been only for $|s| << 1$, however, it will be convenient to keep $|s| << 1$ for the moment, returning to the possibility $|s| \cong 1$ at a later stage of the discussion.

Let $\phi(x, t)dx$ be the probability that the frequency of A lies between x and $x + dx$ at time t. The chance of an individual at random being of the unfortunate homozygous type (A, A) is

$$\int_0^1 x^2 \phi(x, t)\, dx \quad , \tag{5.1}$$

the population being sampled at time t. With many possible deleterious mutations A, all taken to have the same adverse selective factor $s < 0$, occurring at a rate λ per single set of chromosomes per generation (i.e., per

gamete) the total number of mutations arising over a long time interval of T generations in a fixed population of N individuals is $2\lambda NT$. An individual born within the interval has a chance given by the time average of (5.1) of being homozygous with respect to any one of the $2\lambda NT$ mutations,

$$\frac{1}{T}\int_0^1 x^2 dx \int \phi(x,t)\, dt \quad , \tag{5.2}$$

the time integral in (5.2) being over the whole interval T, which is to say from the moment of occurrence of a mutation to the moment of its extinction. This time integral is just the function that in the previous chapter was called $\mu(x)$, so that (5.2) is

$$\frac{1}{T}\int_0^1 \mu(x) x^2 dx \quad . \tag{5.3}$$

This is the chance of the individual in question possessing any one of the $2\lambda NT$ mutations in homozygous form. Hence the number of mutations with respect to which the individual incurs a selective penalty is given by multiplying (5.3) by $2\lambda NT$, viz.

$$2\lambda N \int_0^1 \mu(x) x^2 dx \quad , \tag{5.4}$$

independent of T. Since mutations are injected at $x = x_0 = 1/2N$, which is very small for N large enough, the part of (5.4) for $0 \le x \le x_0$ is negligible. Hence to evaluate (5.4) we require the form of $\mu(x)$ obtained in the previous chapter for $x_0 < x \le 1$. For the present case $h = 0$, this was

$$\mu(x) = \frac{4N f(x_0, 0)}{x(1-x) f(1, x_0)} \exp\left(2Nsx^2\right) \int_x^1 \exp\left(-2Nsz^2\right) dz \quad , \tag{5.5}$$

to sufficient accuracy, where

$$f(x_0, 0) = \int_0^{x_0} \exp(-2Ns\,x^2)\,dx \;\cong\; x_0 = \frac{1}{2N} \quad , \qquad (5.6)$$

$$f(1, x_0) = \int_{x_0}^{1} \exp(-2Ns\,x^2)\,dx \quad . \qquad (5.7)$$

For $s < 0$ we therefore have

$$\mu(x) = \frac{2\exp(-2N|s|x^2)}{x(1-x)} \bullet \frac{\int_x^1 \exp(2N|s|z^2)\,dz}{\int_{x_0}^1 \exp(2N|s|z^2)\,dz} \quad . \qquad (5.8)$$

Counting in the mutation rate λ only those miscopyings for which $2N|s| >> 1$, $\mu(x)$ is negligible unless $x << 1$, in which case the ratio of the integrals in (5.8) is very close to unity and $\mu(x)$ is therefore given to sufficient accuracy by

$$\mu(x) = \frac{2}{x}\exp(-2N|s|x^2) \quad . \qquad (5.9)$$

Inserting (5.9) in (5.4) gives a simple result for the average number of homozygous deleterious mutations possessed on the average by an individual,

$$4\lambda N\int_0^1 \exp(-2N|s|x^2)\,x\,dx = \frac{\lambda}{|s|} \quad , \qquad (5.10)$$

whence the selection penalty incurred by the individual is

$$(1-|s|)^{\lambda/|s|} = \exp -\lambda \;, \quad s << 1 \quad , \qquad (5.11)$$

the same as in the single parent-to-offspring model of Chapter 1, Haldane's result of many years ago.

A dud gene product could in some cases be harmful, either directly so or because a single working gene in heterozygotes might not yield sufficient of a needed product. The corresponding analysis for such a "dominant" situation with $h \neq 0$ follows the same lines as the recessive situation just considered, but with differences of detail. With $x << 1$ as before, the fraction $2x(1 - x)$ of individuals that are heterozygous with respect to a particular mutation is much larger than the homozygous fraction x^2. Hence a particular individual is heterozygous with respect to many more deleterious mutations than it is homozygous, and therefore for h not close to zero the main selective penalty comes from the heterozygous mutations for which (5.1) is replaced by

$$2\int_0^1 \phi(x,t)x(1-x)\,dx \;\cong\; 2\int_0^1 \phi(x,t)\,x\,dx \quad , \qquad (5.12)$$

and (5.4) becomes

$$4\lambda N\int_0^1 \mu(x)\,x\,dx \quad , \qquad (5.13)$$

where the appropriate expression for $\mu(x)$ is now

$$\mu(x) = \frac{2\exp\left[-2N|s|\left\{x^2 + 2h(x-x^2)\right\}\right]}{x(1-x)} \bullet \frac{\int_x^1 \exp\left[2N|s|\left\{z^2 + 2h(z-z^2)\right\}\right]dz}{\int_{x_0}^1 \exp\left[2N|s|\left\{z^2 + 2h(z-z^2)\right\}\right]dz} \qquad (5.14)$$

Once again, the relevant values of x in equation (5.13) are small, because of the $\exp[-2N|s|\{x^2 + 2h(x - x^2)\}]$ factor in (5.14), and for x small the ratio of the integrals in (5.14) is essentially unity, giving

$$\mu(x) = \frac{2\exp\left[-2N|s|\left\{x^2 + 2h\left(x - x^2\right)\right\}\right]}{x(1-x)}$$

$$\cong \frac{2}{x}\exp\left(-4N|s|hx\right) \quad . \tag{5.15}$$

Inserting (5.15) in (5.13) again yields a simple result,

$$8\lambda N\int_0^1 \exp\left(-4N|s|hx\right)dx = \frac{2\lambda}{h|s|} \quad , \tag{5.16}$$

whence, compared to the original population the selective penalty incurred by an individual is

$$\left(1-h|s|\right)^{2\lambda/h|s|} \cong \exp\left(-2\lambda\right) \quad , \quad |s| << 1 \quad . \tag{5.17}$$

Except that the mutation rate is now for both chromosome sets, 2λ, the outcome is the same as before.

The form (5.9) for $\mu(x)$ shows that in the recessive case $h = 0$ deleterious mutations do not penetrate significantly beyond $x = \bar{x}$, with $\bar{x}$ given by

$$2N|s|\bar{x}^2 = 1 \quad , \tag{5.18}$$

while (5.15) shows that in the dominant case $h \neq 0$ penetration cannot proceed significantly beyond $x = \bar{x}$, with $\bar{x}$ given by

$$4Nh|s|\bar{x} = 1 \quad . \tag{5.19}$$

The exponential factors cut off sharply for $x > \bar{x}$. The explicit path $x(t)$ followed by a particular mutation starts at $x = x_0 = 1/2N$, $t = t_0$. Due to stochastic effects the path wanders around for a number of generations without x exceeding $\sim\bar{x}$, until eventually at some time t, $x(t) = 0$ and the mutation is then extinct. We can ask how large the time difference $t - t_0$ can be before extinction occurs, the largest time differences occurring for mutations where stochastic fluctuations happen to increase x to order $\bar{x}$.

In the majority of cases where deleterious mutations become extinct without x increasing to order $\bar{x}$ their behaviour is controlled by stochastics not by selection, with the probability of going in a generation from frequency x to a frequency in the range x' to $x' + dx'$ given by the infinitesimal propagator

$$\sqrt{\frac{N}{\pi\, x(1-x)}}\ \exp\left[-\frac{N(x'-x)^2}{x(1-x)}\right]dx' \quad , \tag{5.20}$$

which for $x << 1$ can be written to sufficient accuracy as

$$\sqrt{\frac{N}{\pi\, x}}\ \exp\left[-\frac{N(x'-x)^2}{x}\right]dx' \quad . \tag{5.21}$$

Defining Δx by

$$\int_x^{x+\Delta x} \exp\left[-\frac{N(x'-x)^2}{x}\right]dx' = \int_{x+\Delta x}^{\infty} \exp\left[-\frac{N(x'-x)^2}{x}\right]dx' \quad , \tag{5.22}$$

which gives

$$\operatorname{erf}\left(\sqrt{\frac{N}{x}}\,\Delta x\right)=\frac{1}{2} \quad \text{, that is,} \tag{5.23}$$

$$\Delta x = 0.485\sqrt{\frac{x}{N}} \;\cong\; \frac{1}{2}\sqrt{\frac{x}{N}} \quad , \tag{5.24}$$

we can say that the gene frequency shifts in a generation from x to either $x + \Delta x$ or to $x - \Delta x$ with equal probability $1/2$.

The situation is like a one-dimensional diffusion problem with mean free path Δx that depends on the square root of the diffusion distance x. As in all diffusion problems, the number of steps, that is, generations, required for the diffusion distance to change from x to either zero or $2x$ is

$$\sim\left(\frac{x}{\Delta x}\right)^2 \;\approx\; 4Nx \quad . \tag{5.25}$$

Hence the circulation time of a deleterious mutation is of the order of $4N$ times the largest frequency reached along the path $x(t)$ which the mutation happens to follow. The largest x that can happen because of adverse selection is $\sim\bar{x}$ with $\bar{x}$ given by (5.18) or (5.19) according to the value of h. The maximum circulation times in generations are therefore

$$\sqrt{\frac{8N}{|s|}} \quad \text{if } h=0\,, \qquad \frac{1}{h|s|} \quad \text{if } h \text{ is not small.} \tag{5.26}$$

For $8N = 10^6$, $|s| = 10^{-2}$, the maximum circulation time is $\sim 10^4$ generations for recessive mutations, but only $\sim 10^2$ generations for dominant mutations. Except in small population groups, recessives circulate much more slowly than dominants.

A complacent attitude to the expression $\exp -\lambda$ for $h = 0$, or $\exp -2\lambda$ for $h \neq 0$, in the fitness of a species would be to say that the standard with respect to which these factors have been calculated is that of an initially pure line

population, and that no actual test of fitness can arise because by the time defects have arisen, the initial population no longer exists. Provided the deleterious mutations have $|s| << 1$ this is largely true. Every individual after a time interval of order (5.26) has either $\lambda/|s|$ recessive defects or $2\lambda/|s|$ dominant defects, with selection only bearing down on fluctuations in these numbers, fluctuations which are of order $(\lambda/|s|)^{1/2}$. For $|s| = 0.01$, $\lambda = 0.3$, $(\lambda/|s|)^{1/2} \cong 5$ and $(1 - |s|)^5 \cong 0.95$, so that selective penalties on the less fortunate of the community are only about 5 percent. It is this selective penalty that prevents continuing mutations from making the situation progressively worse. This is for mutations that satisfy $2N|s| >> 1$, which was assumed throughout the above discussion. The complacent view is that such penalties are not very onerous on the disadvantaged. If the most speedy humans can run a mile in 4 minutes, to be 5 percent worse at 4 minutes 10 seconds should not be too much of a handicap to bear. And to have a 5 percent less chance than the average of leaving surviving descendants would not be felt a grievous burden by most humans either. But there is another darker side to the matter implied in the mathematics.

The frequent mutations that must render genes seriously defective, while possibly carrying little penalty in heterozygotes, are likely for important genes to impose a grave penalty on homozygous individuals having both genes defective on both chromosome sets. With such a situation lethal or near lethal, especially for creatures in the wild without the technological support which humans enjoy nowadays, $s \cong -1$. The average number of such seriously deleterious defects would still be $\lambda/|s|$ per individual, with λ as their rate of occurrence per gamete. If λ continued to be ~0.3 we would thus have about one individual in three afflicted by an essentially lethal genetic defect. In such a situation the entire load of maintaining the genetic integrity of the species falls on the unfortunate one individual in three, a situation that in the human case at least cannot be contemplated lightly.

All the work of Chapter 4, on which the derivation of (5.10) depended, appeared at first sight to be based on $|s| << 1$, so that we have to reexamine the premises of Chapter 4 before accepting the implications just mentioned. Reference back will show that three approximations involving

$$y = s\,\frac{x(1-x)\left[x+h(1-2x)\right]}{1+sx\left[x+2h(1-x)\right]} \tag{5.27}$$

were made. The first was to replace the denominator of (5.27) by unity. For deleterious mutations with $x << 1$ this evidently does not require $|s| << 1$, so that for deleterious mutations this first approximation does not place any restrictive condition on $|s|$. In expanding the left-hand side of (4.7) by a Taylor series a term $\frac{1}{2}(t - t')^2 y^2 \partial^2\varphi/\partial x^2$ was neglected. This is justified because for $h = 0$, $y \cong sx^2$ and so for $x << 1$ the term is small irrespective of $|s|$. For advantageous mutations with x of order unity it would be otherwise. For advantageous mutations $s << 1$ it is necessary to justify the former approximations.

The same situation arises for the third approximation, which occurred in passing from (4.8) to (4.9), when the $(dy/dx)^2$ term in $(1 + \overline{t-t'}\,dy/dx)^2$ was neglected. For $y \cong sx^2$, this $(dy/dx)^2$ term is of second order in x, and so for $x << 1$ the neglect is again justified. Just the same neglect of a $(dy/dx)^2$ term occurred in (4.9), in the expansion

$$\exp\left[-\frac{2N(x-x')^2\,{}^{dy}/_{dx}}{x'(1-x')}\right] = 1 - \frac{2N(x-x')^2}{x'(1-x')}\,\frac{dy}{dx} + \cdots \qquad (5.28)$$

which also turned on $|dy/dx| << 1$. The circumstance that (5.28) was multiplied in (4.9) by $\exp -N(x-x')^2 / x'(1-x')(t-t')]$ prevented values of x' in (5.28) being relevant unless

$$\frac{N(x-x')^2}{x'(1-x')} \leq t - t' \qquad . \qquad (5.29)$$

Since $t - t'$ was a generation or at most a few generations, equation (5.29) requires $N(x - x')^2 / x'(1 - x')$ to be not large compared to unity, whence, provided $|dy/dx| << 1$, the second-order term in (5.28) can be neglected.

Hence, for deleterious mutations whose frequencies necessarily remain small compared to unity, all the work that led to the partial differential equation (4.20) continues to hold good for $|s| \cong 1$, and hence the somewhat grim aspects mentioned above cannot be avoided on mathematical grounds. Besides which, our deductions to this point have a considerable ring of truth about them. Trials of strength and games of skill turn on remarkably small advantages, showing that our deduction of a 5 percent swing about the

average, contingent on fluctuations in the number of defects with $|s| << 1$ from one individual to another, is not at all far short of the mark. So too, unfortunately, do examples of the birth of seriously disadvantaged individuals with $|s| \cong 1$ spring easily to mind. A proportion of one in three such cases is too high for modern human society, but in the much harsher conditions of prehistoric humans it probably would not be too far short of the mark either. The time scale (5.26) for the onset of the lethal mutations for the relevant case $h = 0$ is only $\sim(8N)^{1/2}$ when $|s| \cong 1$. For an inbred village of 200 adults, $(8N)^{1/2} = 40$ generations. If nonsurviving juveniles under primitive conditions were included, the total population of such a village might be four to five hundred persons. A generation interval is not the time for which individuals live but the time from birth to reproductive age, which for humans could be as short as 15 to 20 years, so that 40 generations implies a time span of 600 to 800 years. This, it will be recalled, was a maximum estimate, made for the deleterious mutation of longest circulation. For deleterious mutations on the average, a circulation time about a half to a third of $(8N)^{1/2}$ would be appropriate, say two to three centuries for our village. Starting from an entirely healthy situation with no lethal recessives, a bad situation affecting up to one offspring in three would arise in substantially less than a millennium.

We are now in a position to make two interesting deductions and to offer a number of sociological observations. Defects observed among the populations of inbred villages are as much likely to be mental as physical, as the terms "village idiot" and "country bumpkin" imply. From this we could deduce that as many genes must be employed in the action of the brain as in promoting the more physical properties of the body, a deduction which in recent years has been shown to be true. The second important point which can be made is that not all mammalian DNA could possibly be utilized in the production of working proteins. If it was, λ would ~10 and the genetic load $\exp -\lambda$ would be impossibly heavy. It is a probably correct speculation that the amount of expressed DNA is as large as it can be without deleterious mutations becoming impossibly destructive.

There is a strategy which populations can adopt for dealing with the difficulties discussed above. Divide a total population with $N = 10^6$, say, into subgroups each with $N = 100$ and restrict mating to individuals within the same subgroup. The effect is greatly to speed up the circulation of deleterious mutations. Instead of circulating in a time scale of 1000 generations for

$N = 10^6$, circulation in each subgroup occurs in only ~10 to 20 generations. Even for such a long-lived species as ourselves, all correlation between the serious deleterious recessives circulating in our subgroup and those circulating in another will be gone after only a few centuries—the recessives will be different in different subgroups. Now mix the subgroups, ensuring that individuals from the same subgroup do not mate together. All progeny will then be heterozygous for the recessives and no lethal cases will occur. This happy situation will persist for up to ~1000 generations when it will be necessary once again to fragment the larger population into small subgroups. At the expense of ~10 generations of bad genetics, ~1000 generations of good genetics, if forthcoming, is an immense gain.

Everything so far in this chapter has been for mutations with selective factors such that $2N|s| >> 1$. Reference to Table 4.1 shows that minor mutations with $2N|s| \lesssim 1$ have a probability of penetrating a species not much different from $1/2N$, the probability for penetration by a neutral mutation. Write ξ for the rate per generation per chromosome set at which mutations with $2N|s| \lesssim 1$ arise. Then the total number occurring per generation in the whole population is $2N\xi$, of which ~ξ become fixed. Hence in G generations ~ξG such mutations become fixed, so that the species acquires a steadily growing penalty

$$(1-|s|)^{\sim \xi G} \cong \left(1 - \frac{1}{2N}\right)^{\sim \xi G} \cong \exp\left(-\frac{\xi G}{2N}\right) \quad , \qquad (5.30)$$

the mutations for which ξ is determined having $2N|s| \approx 1$. If similarly to λ we rate $\xi = 0.3$, then for a population of $5 \cdot 10^5$ individuals there is a significant decline in $G = 2N/\xi \sim 3 \cdot 10^6$ generations, which for a typical mammalian species is about 10^7 years, significantly less than major evolutionary time scales of several hundred million years. Hence if ξ is as high as 0.3, species with population numbers not exceeding 10^6 must either collapse on such time scales due to a persistent erosion of their genetic material, or new uneroded genetic material must be acquired in some way. In relation to the discussion of the next two chapters, the latter is an interesting possibility. It would explain why so much of DNA goes unused. Unexpressed DNA could be old eroded genetic material that has been discarded as new material has been acquired. The excess of unused over used DNA, a ratio of

perhaps 20 to 30 to 1, would then be a measure of the antiquity of the evolutionary process itself, the latter being ~$20 \cdot 2N/\xi$, a hundred million generations for $2N \cong 10^6$, $\xi \cong 0.3$.

Returning to much shorter time scales, humans need no encouragement at all to form themselves into small inbred groups. All our instincts seem directed toward producing an immense fragmentation of the total human population. The typical size of inbred groups, whether the hunting groups of Neolithic humans, the medieval village, the more modern tribe or clan, or an aristocracy, is about 500 persons. So too are scientific academies and houses of parliament. Given half a chance this is what human psychology always seems to favour—a situation that is clubbable. Allowing for juveniles who do not survive to maturity, early groups with totals of about 500 would have had an effective value of N around 200. So long as man's penchant for subdivision was supported by adequate geographical separations, well and good, nothing very violent could happen. But artificial subdivision due to tribal structure, or as in medieval times due to political fiat, must sooner or later become explosively unstable, as soon as some perturbation of society causes several contiguous subgroups to intermingle. Instability arises because the progeny of parents from different subgroups would be free of homozygous debilitating recessives, since the adverse mutations possessed by one parent would mostly if not wholly be different from those of the other parent. The outcome would be a generation of far more competitive individuals, with the likelihood that geographical expansion would take place, sucking in more and more subgroups into the mixing pot, thereby generating a kind of detonation wave that would exhaust itself only when impassable geographical boundaries were reached.

Many examples come to mind, of which the almost instantaneous break up of medieval Europe at the end of the fifteenth century is excellently documented. The medieval population was largely rural, with severe legal restraints imposed against the free movement of people. The longer the subgroups in the villages were forcibly kept apart the more unstable the situation became, with its dénouement in Britain coming with the loss of the French possessions and the ensuing War of the Roses. The resulting biological explosion was that we associate nostalgically with Shakespeare and Tudor England.

There must be few people who are not fascinated in some degree by history. In their dedication to getting the facts of history as correct as

possible—no easy task in view of those in all ages who attempt to muddy the waters—historians serve a crucial function in society. Our lives are experienced subjectively largely as events that are past. The notion that we live "in the present" is an illusion, for no sooner do we experience an event than it is past already. As a mathematician might put it, the "present" has measure zero. No wonder then that it is important to have the past as correct as possible. Even so, in spite of the great fascination of it all, I never had a strong impulse to study history professionally, on duty as it were, essentially because I felt that historical studies raised a whole lot of interesting questions which were not answered in a satisfactory way. I simply could not believe that it all boiled down to policies formulated by the individual rulers of communities who pop up and down throughout the pages of history like a troupe of jack-in-a-boxes.

I began to feel better about it when I came to interpret history in regard of the development of technology. The march of technology seems always to have been forward, unlike nations which flourish for a while and then decline. But technology could not be everything. It did not explain why the Hellenistic Greeks, who had been so dominant in the days of Alexander, came to be subjugated a couple of centuries later by the Romans. Nor how it came about that in the thirteenth century the Mongols were suddenly able to explode out of Asia and sweep all opponents before them. Such convulsions fall easily into line, however, when the biological considerations of the present chapter are brought to bear. The Hellenistic Greeks expanded in the Mediterranean by establishing sea-bordering colonies that did not expand much into their hinterlands, and which therefore became largely closed communities, each mating persistently among its own inhabitants and so incurring the genetic penalties described above. The Romans, on the other hand, emerging from a forcible intermingling of tribes, developed an extensive hinterland. In terms of the cyclic process of inbreeding and outbreeding, the Greeks and Romans seem to have been at opposite phases, the one incurring biological penalties, the other in the expansive process of being freed from them.

It is remarkable that our subjective preference for what seems desirable in life and what seems disastrous should run so exactly counter to the biological situation. Our preference is overwhelmingly for a secure life, surrounded by friends and their families, of whom we would hardly number more than a couple of hundred. Daughters and sons almost inevitably marry within the club, seeking to preserve material possessions and common cultural values.

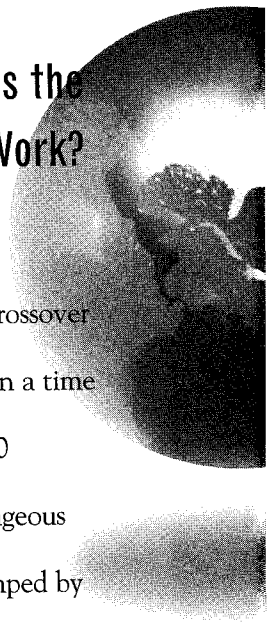
Comfortable and cozy, in contrast to population upheavals following defeat in war, in contrast to migrants quitting their home communities in sorrow due to poverty or as outcasts due to nonconformity over some issue or other. Yet it is the migrants who are traveling toward a future in which, by genetic mixing, their progeny will come to dominate the world.

The biological problem ironically becomes more acute the higher the social class, for the higher the class and the wealthier its members the more they are able to indulge their antibiological preferences. Particularly vulnerable in times gone by have been royal households. Although free to decide their mating partners, kings and princes opted overwhelmingly for brides who contributed possessions and influence, thereby limiting choices to an in-group typically of the order of a hundred, and so with mathematical certainty ensuring degradation on a time scale of a century or two. There have been exceptions with notable results, as with Robert of Normandy's infatuation for Herleva the burgher's daughter, from which frowned-on liaison came William the Conqueror. William himself did not perceive the biological lesson, however, and within a century the line of his immediate descendants ran out. Thereafter the Plantagenet house had a comparatively long run for its genes, from the mid-twelfth century to the death of Richard III in 1465. The Tudors then managed a century and a half, the Stuarts a century, time spans inevitably dictated by our formula (5.26).

Modern populations are so large, with N usually exceeding 10^7 and sometimes even 10^8, that one might think populations today must inevitably be living in a favourable period of almost total outbreeding. Yet those populations with histories of immigrant flows like Australia and the United States, and those which recently have been greatly stirred in the aftermath of war like Germany and Japan, are performing so well in comparison with less mixed populations like the British that I have to suspect that some of the genetic effects of inbreeding still linger on in the world's more static populations. A glance at traffic flows on British motorways does not suggest a static situation of course, but the immense difficulty which the British have in changing houses between one place and another suggests a population that is still rather rigidly rooted in its homes, its classes, its manners of speech, and its clubs and pubs. The British population is certainly not inbred in anything like a medieval sense, but modern margins in sport and commerce are so fine that a nation only needs to be a little subpar genetically for the effects to become rather obvious.

Chapter 6

How Far Does the Neo-Darwinian Theory Work?



A sexual system of reproduction with crossover decouples the selective effects of genes on a time scale that is usually not greater than ~100 generations. Comparatively rare advantageous mutations can thereby avoid being swamped by much more frequent bad mutations. A penalty has to be paid, however, when the advantages conferred by the mutations are small, as they are commonly supposed to be in neo-Darwinian

theory, the penalty being that most small advantages are lost by stochastic effects, only a fraction ~s succeed in penetrating a species. But this penalty must be paid, since otherwise species could not evolve at all in a positive sense.

When a species is developing new patterns of behaviour, advantageous changes must necessarily be small, because the genetic material of the species cannot anticipate what a new pattern of behaviour is going to be in advance of it being adopted—the species must edge by slow degrees toward what is new. But in a situation where a species is adapting to an environment it has experienced before, the situation could conceivably be otherwise. Genes may have changed over an intervening period since the environment was last encountered, but provided the intervening period was not too long by only a few base-pair changes on the DNA. Such comparatively minor changes may be reversible, because of the species being already at the verge of what is genetically required for readaptation to the old environment. Large advantageous changes brought about by as little as a single base-pair change on the DNA are then conceivable. Such cases are not evidence, however, that advantageous changes can be large when adaptation with respect to an entirely new environment is in question. Finding the neo-Darwinian theory to work only weakly in the general situation, my impression is that some evolutionists have sought to speed things up by wrongly considering cases where species are only coping with environmental conditions they have experienced before, so that memory is being misinterpreted as discovery.

The peppered moth, *Biston betularia*, so called because it has speckled black and white wings, is frequently misinterpreted in this sense. A dark form of the moth was first noticed near Manchester in the mid-nineteenth century. Thirty years later it had outnumbered the light form of the moth, which had hitherto been more common, as much as a hundredfold in the area. The explanation offered for this phenomenon was that the dark form of the moth was not as conspicuous to bird predators as the light moth against trees which were blackened by the soot from the burning of coal in a heavily polluted area.

The dark form of moth has a working gene which produces the pigment melanin, a gene that has become inoperative in light-coloured moths. For convenience of discussion, suppose selective properties to be so severe that a juvenile moth born light cannot survive to maturity in an environment of dark trees, and that a juvenile born dark cannot survive in an environment of light trees. Now suppose the environment to oscillate, first with dark trees,

then with light, and so on, the switches taking place through phases of several years in which both light and dark trees are present. What happens?

Start in the environment of dark trees with all melanin-producing genes in working order. The rate at which the genes become inoperative is ~10^{-6} per gamete, so that for a population of M juvenile moths about $2 \cdot 10^{-6}$ dud genes are injected into the population at each generation. The dud gene being recessive (i.e., the case $h = 0$) its severely deleterious effect shows up only in homozygous juveniles, of which there are Mx^2, where x is the frequency of dud genes. Hence with the effect lethal in those homozygous individuals, ~$2Mx^2$ dud genes are eliminated in each generation. Setting this elimination equal to the injection rate gives $x \cong 10^{-3}$, so that for $M = 10^8$ as an example about 100 moths are born light in each generation, despite the property being lethal in the environment of dark trees.

Permitting the old population of mostly dark moths to survive for several generations as a switch is made, now let the dark trees give place to light trees. Although the old population with a frequency ~10^{-3} of inactive genes can produce only one light moth in a million, the circumstance that an immense number of juveniles is produced means that some light moths continue to be born, even though as the trees become light, avian predators produce a spectacular decline of the adult population of dark moths. With dark-coloured juveniles being picked off in mass on their way toward maturity, the light moths come through to maturity in far greater proportion than the ratio of one to a million in which they are born. Selection against dark moths attaining maturity eventually becomes intense enough for the light ones to find each other, and for mating to take place between them. When this happens there is an explosive production of light-coloured juveniles, with the consequence that the frequency x of the inactive gene rises with great rapidity from its former value ~10^{-3} to unity. Notice that it is the capacity of adults to produce many juveniles that saves the day for the moths. If adults produced only a few juveniles, light moths would hardly be born at all as the population of dark moths fell away, and so the light moths would never find each other, and the species would become extinct. From this example we see, therefore, why creatures exposed to drastic oscillations of the environment need to produce immense numbers of juveniles—in order that rare properties continue to show themselves as the population falls.

Now consider a switch back from light to dark trees, again permitting a number of generations of the moths to occur during the interval in which the

switch is made. For survival now, it is essential to re-activate the melanin-producing gene, and to do so before the switch of the trees is completed. The moth has two advantages on its side. Provided the trees have not been light-coloured for more, say, than 100,000 years, it is not likely that the inactive gene will be carrying more than one defect, one base pair on the DNA needing change. The other advantage is that, if the one base pair can be restored, the resulting melanin production is a dominant property, with a working gene on one chromosome set sufficing to make the moths dark again. Taking the probability of repairing a particular base pair as $\sim 10^{-9}$ per gamete, the chance that a juvenile at random returns to the dark form is $\sim 2 \cdot 10^{-9}$, whence for, say, 10^8 juveniles the dark form is recovered in only a few generation. Then, with melanin production dominant, the first mating of the dark form produces a flood of dark juveniles, with a consequent quick return to the previous situation.

Provided inferior genes are separated from a superior form by only a single base pair, as in the example just considered, a large advantageous mutation can be found, by populations as large as 10^8 in a few generations and by species with populations of order 10^6 in a few hundred generations. But when genes are not poised on the very edge of important selective significance, when they are separated from important advantage by two or more base pairs, the advantage cannot be found. In the above discussion of the peppered moth, suppose that after the first switch from dark to light trees, the situation were maintained for a very long time before the second switch back to dark trees. During the long episode of light trees further damage to the melanin-producing gene would occur without selective penalty. Suppose the further damage to be such that every melanin-producing gene develops a second base-pair error, so that when eventually the trees switch back from light to dark all genes have two base-pair errors which must then be set right if melanin production is to be resumed and the moths survive. The chance of setting a particular base pair right in a particular gene in G generations is $\sim 10^{-9}G$, and the chance that two base pairs are set right in the same gene is $\sim (10^{-9}G)^2$. For a total of $2N$ genes in a population of N individuals the probability of one emerging in a repaired condition after G generations is therefore $\sim 2N(10^{-9}G)^2$, which to be of order unity requires $G \cong 10^9/(2N)^{1/2}$. A mammalian population with $2N = 10^6$ would require $G \cong 10^6$ generations, which is so long that further errors would accumulate in every individual before the two base pairs were corrected in any individual. For $2N = 10^8$,

about 10^5 generations would be required—far too long to save moths in a practical situation.

From this example we can say that for any discarded gene properly to be recovered in a practical situation, it is necessary that the genes in question shall not differ from a working condition by more than one or two base-pair errors. Once genes drift by more than this from a working condition they can be considered to have gone permanently dead, thereby explaining an otherwise mysterious conclusion of classical biology, that once species become highly specialized they tend to become extinct. A highly specialized species gains a major advantage so long as environmental conditions favouring its precise mode of adaptation persist. But the advantage so gained tends to make some gene properties redundant that were previously necessary for survival. The properties in question, no longer protected by natural selection, develop errors. Once the errors accumulate to several base-pair mistakes per gene, the original properties become irrecoverable, and should the environment change so that the original properties are needed again, the species plunges to disaster and becomes extinct.

I am told by zoologists that the growth of fur is controlled by a single gene, which in humans has gone inactive. It seems rather unlikely that a sufficient number of generations has elapsed since the gene went dud for more than a single critical base-pair error to have yet accumulated. If so, the chance of any human child being born in a fully furred condition must be $\sim 10^{-9}$. About one such child would be born per century in Europe. The usually quoted example is Adrian Jeftichjew, the so-called Russian dogman. If environmental conditions ever demanded that humans should return to a furred condition, given sufficient positive selection and a millennium or two in which to operate, fur is probably recoverable, when no doubt our present unfurred condition would be seen as a temporary unfortunate episode that was not spoken about in polite society.

The extreme rarity with which furred children appear in the human population, even with a minimal error in the relevant gene, shows by a practical example how impossibly rare it would be for a gene with several errors to be again set in a working condition. The situation for three or more errors would be rare beyond any possibility of experience, while the situation for a hundred or more errors would be beyond consideration even in the most abstract sense. Yet there are of the order of a thousand genes in the simplest biological systems, and many more than a thousand in the higher plants and

animals, that each demand more than a hundred base pairs to be just so in order that they be in a working condition. The problem for the neo-Darwinian theory is, not to explain situations like the peppered moth involving only a single error on a single gene, but the evolution of thousands of genes each requiring a specific arrangement of hundreds of base pairs if they are to function at the level of even the simplest organisms.

Let me give a few examples. The process of translating base pairs on DNA into a protein involves various kinds of RNA molecules which act as intermediaries, with transfer RNA (or t-RNA) molecules, establishing a correspondence between triplets of base pairs on the DNA and the appropriate amino acids in the protein. If a wrong t-RNA got into the system, giving a wrong amino acid response to a triplet of base pairs, the resulting proteins from all genes would be garbled, and for highly sensitive proteins like the enzymes the situation would be disastrous. Hence little or no latitude is permitted for the t-RNAs, and so the nucleic acid which codes for the t-RNAs can have very little latitude indeed, with hundreds of base pairs involved for each t-RNA.

Because of redundancy in the genetic code it is not possible to work backward from the amino acids of a protein to the triplets of base pairs which coded for it—on the average there are about three different triplets coding for the same amino acid. Even though natural selection may hold a protein to a unique chain of amino acids, shifts of base pairs can occur provided they do not go outside the redundancy permitted by the genetic code. Such selectively neutral variations in the DNA are found in the case of the protein histone-4, which has a chain of 102 amino acids. In humans about thirty distinct genes code for histone-4, apparently because there is need for a large amount of this particular protein to be produced. The genes have variations in their base pairs, but the variations are all of the kind permitted by the redundancy of the genetic code. They all code for the same amino acid chain. Other variations that did not code for the same amino acid chain must surely have occurred but were stamped out by natural selection. Essentially, the same amino acid chain being found also in other animals and even in plants, we have a case in histone-4 where more than 200 base pairs are conserved across the whole of biology. The problem for the neo-Darwinian theory is to explain how the one particular arrangement of base pairs came to be discovered in the first place. Evidently not by random processes, for with a chance 1/4 of choosing each of the correct base pairs at random, the probability of discovering a segment of

200 specific base pairs is 4^{-200}, which is equal to 10^{-120}. Even if one were given a random choice for every atom in every galaxy in the whole visible universe, the probability of discovering histone-4 would still only be a minuscule $\sim 10^{-40}$.

The histones are a small class of protein which play a critical role in the process of cell division. Except at times of cell division the chromosomes exist freely and separately in the cytoplasm of a cell. With the approach of cell division, the chromosomes are first duplicated and then condensed into a compact, much more visible structure known as chromatin, which can be stained by suitable dyes to make it accessible to microscopic examination. The histones appear to provide physical support for the chomosomes in this process of condensation and in the complex maneuvers, which then lead to crossover and cell division. A form of histone-4 with rogue properties that led to wrong crossover or to chromosomes being torn during cell division would clearly be lethal, just as wrong t-RNA molecules would be lethal. So can one plausibly explain the observed uniqueness of histone-4. Without histone-4 being exactly right, cells could not divide properly and nothing in the whole biological system would work correctly.

Faced with this situation, neo-Darwinians retreat into an untestable position. Histone-4 evolved step by step they characteristically argue, with each step requiring no more than a single base-pair change. To the objection that step-by-step evolution was not possible because histone-4 is an all-or-nothing case, they reply by admitting that, while in the present situation this may be true, the situation as it once was differed in this respect. In a more primitive situation, histone-4 evolved step by step it is claimed, thereby retreating neatly into the unknowable and untestable, a device which, however, is not logically tenable because primitive systems without sexuality and crossover cannot evolve.

The issue properly within the range of science is whether the basic genetic features of terrestrial species—enzymes, t-RNA molecules, the histones, the genetic code itself—are indigenous to the Earth at all. Biologists have sometimes said that they see no advantage in transferring the problem of the origin and evolution of life onto a cosmic stage because the deeper problems would still have to be solved. I find this point of view strange. When in science several paths are open to investigation it makes sense to try the apparently simplest one first. But if what at first appeared the simplest path turns out to lead into a morass, it then makes sense to investigate other paths. The aim of science should be to discover the correct path, not to adhere to an incorrect route because at first glance it seemed simplest.

Microorganisms and genetic fragments are extremely space-hardy. They can withstand very low pressures and wide fluctuations of temperature, and they are remarkably resistant to radiation damage, especially if protected by a little shielding material against ultraviolet light. The Earth's atmosphere would permit space-incident biomaterial to make a soft terrestrial landing without damage occurring due to excessive heating, provided the biomaterial were in the form of small particles with diameters less than ~100 μm. The physical conditions therefore permit both microorganisms and the eggs and sperms of lower animals to be incident from space, as well as viruses and viroids, which can add further genes to species already established here on the Earth.

The genetic makeup of a plant or animal incident from space would not initially yield a close adaptation to the terrestrial environment. Many present-day species possess marvelously subtle adaptations of the kind which delight the makers of the excellent nature films shown frequently these days on television, adaptations in which a plant or animal makes special use of some fine detail of the environment—it secures a niche as one says. Space-incident organisms could hardly possess such intimate relationships as are actually found. Nevertheless, a general broad correspondence with the environment could quite well arise, for if one imagines the external incidence of genetic structures covering a very wide range of properties, considerably wider than could survive here on the Earth, then the terrestrial environment would automatically select out those genetic associations which happened to permit survival on our planet.

The nature films shown on television, despite their technical excellence, are likely to yield the wrong impression that all terrestrial life is subtly adapted to its environment. In some cases it is, in others it isn't. By concentrating on well-adapted cases, a false impression is created, the same false impression that has been created by Darwinians from 1860 onward, the recipe being always to concentrate on the successes and never to mention the failures. Microorganisms in particular are often quite seriously disadapted from their environment, as for instance wide divergences from optimum temperatures. Indeed, it would be more correct to say that microoganisms exist wherever they can gain a toehold, regardless of adaptation.

It is a mistake to suppose that science is an unswerving pursuit of objective truth. Partially it is, but only to the extent that the truth does not turn out to contradict what has already been taught in the educational process. Students in organic chemistry still learn that in 1828 Friedrich

Woehler destroyed the old doctrine of vitalism by preparing urea from ammonium cyanate. But the latter almost surely had its origin in the action of denitrifying bacteria in the soil, so that the claimed production of a biological product from nonbiological sources was very likely wrong, and could have been seen to be wrong from Pasteur onward. Mistakes of scientific history are still more ineradicable. Few students are ever informed that the concept of evolution through natural selection was under discussion fully a quarter of a century before Darwin's book *On the Origin of Species*. Ironically, the theory was then rejected for what was considered a failure of species to adapt to the environment.

Writing in the mid-1830s, Edward Blyth was well aware of the precision of adaptation at the level of varieties of species, but not above the level of species he maintained. The argument he gave was a powerful one, and in the later enthusiasm for the Darwinian theory it was never answered properly. Most species are limited to a geographical area, with good adaptation to the conditions well inside the area but with less and less good adaptation toward its boundaries. Why, Blyth asked, if species can evolve to the great extent that would be needed to explain the differences between genera, families, orders, and classes can they not evolve to the lesser extent that would maintain adaptation to and beyond the boundaries of their respective areas? Instead of doing so, however, species stay obstinately fixed, disappearing as the limits of their habitats are reached. According to Blyth, this fact, which was the rule not the exception, proved that the capacity of species to adapt must be limited, making what today we call the Darwinian theory (but which Blyth considered in 1837) untenable.

This argument of Blyth's was strong enough to hold back the theory of evolution by natural selection for more than two decades, causing Darwin not to risk open confrontation. Darwin retreated into a protracted study of barnacles instead, and it was Alfred Russel Wallace who eventually took up the challenge on behalf of evolutionists, who included Robert Chambers as well as Darwin. Chambers was the first person so far as I am aware to propose that land-based animals had evolved from fish. Wallace was in the position of having to earn a living in a subject which in those days offered few opportunities to any but persons with private means. He hit on the idea of combining his interest in biology with the need to earn a living by collecting specimens, which were then sold to museums and private individuals. In the course of his wanderings in the Amazon Valley and later

in the Dutch East Indies over a period from 1847 to 1862, Wallace is said to have discovered 30,000 new species, which meant that his knowledge of field zoology became immense. So many of the intricate adaptations of the kind we see today became apparent to him that evolution could be their only explanation. Wallace then extended the evidence for evolution that he could see in present-day species to the recent fossil record. In the paper published in 1855 he was able to show to the satisfaction of even such a sceptic as the geologist Charles Lyell that present-day species had been preceded by similar species in similar geographical areas, Wallace's law as it eventually became known. Noting the profound effect Wallace's arguments were having on Lyell, Darwin turned back from barnacles to evolution, but still not out in the open. Still missing from Darwin's concepts was what later became called the principle of divergence. Eventually, however, in June 1858, Wallace sent a manuscript to Darwin that explained the principle of divergence so clearly that Darwin was at last able to begin his preparations for *On the Origin of Species*, which repeated in 490 pages what Wallace's manuscript had said in 10 pages.

But the objections to the theory of evolution by natural selection had not really been answered, and by 1870 Wallace had come to realize that something in addition was needed. Thus to Wallace, as to Lyell and to Blyth long ago, there was something right about evolution by natural selection and there was something wrong. This balanced position, which was the correct one, never had a fair hearing from 1870 onward however, because the developing system of popular education provided an ideal opportunity for zealots who were sure of themselves to overcome those who were not, for awkward arguments not to be discussed, and for discrepant facts to be suppressed. This was because popular education created a body of students who, like Wallace himself, had of necessity to make their ways in life, and because it is only students from privileged backgrounds who can afford to adopt views contrary to what they are told.

There was nothing wrong in Wallace's use of the recent fossil record but attempts to use the more distant fossil record in order to investigate wider evolutionary connections has not been similarly successful. From 1860 onward the more distant fossil record became a big issue, and over the next two decades discoveries were made that at first seemed to give support to the theory, particularly the claimed discovery of a well-ordered sequence of fossil horses dating back about 45 million years. Successes like this continue to be

emphasized both to students and the public, but usually without the greater failures being mentioned. Horses according to the theory should be connected to other orders of mammals, which common mammalian stock should be connected to reptiles, and so on backward through the record. Horses should thus be connected to monkeys and apes, to whales and dolphins, rabbits, bears. ... But such connections have not been found. Each mammalian order can be traced backward for about 60 million years and then, with only one exception, the orders vanish without connections to anything at all. The exception is an order of small insect-eating mammal that has been traced backward more than 65 million years, through the mysterious event which extinguished about half the genera of all animals including the large dinosaurs, including indeed every animal weighing more than 50 pounds of whatever species, and even including microscopic animals living on the sea bed.

The story is the same for other classes of animal, the case of insects being particularly well documented. Orders of insects can be traced back over 200 million years for mayflies and dragonflies and about 300 million years for cockroaches, grasshoppers, and locusts. The striking feature of these long records is that they contain little evidence of change; and they too fade away to nothing instead of connecting to other orders of insects. The theoretical presumption of evolution for a common ancestor is not there in the insect record, just as it is not there for mammals, or for any other class of animal or division of plant. Still less is there evidence of evolution connecting different classes and divisions, subkingdoms or kingdoms. In 1860 it could be claimed with some plausibility that the record was seriously incomplete, and it could therefore be hoped that with increasing knowledge the more distant connections postulated by the theory would eventually be found. They have not been, and since geology has expanded enormously in scope over the past century, it now seems unlikely that the postulated connections will ever be found.

One still hears talk of the incompleteness of the record, but fossils of many insects continue smoothly throughout the period some 60 million years ago when the mammalian record fades away. To the excuse sometimes offered that insects fossilize better than mammals, the reply is that, if insects fossilize so well, why is it that the insect record also fades away before connections between the insect orders are found? Why is that crustacea, shrimps for example, continue smoothly through the period some 350 million years ago when the insect record fades away?

The external incidence model, combined with what has been learned from the mathematical results of earlier chapters, copes with all these difficulties. As we have noted, external incidence can be expected to give only coarse fits between species and the environment. Fine-scale adaptation, which so impressed Wallace and his contemporaries, comes from the ability of species to optimize adaptation with respect to single base-pair changes. Wherever a gene can improve performance by a single base-pair change, mutations will find the change and selection will operate to promote it. What mutations cannot do is to find improvements which demand the simultaneous change of several base pairs. Once the range of improvements conferrable by single base-pair changes have become exhausted, a species cannot evolve further. It becomes limited in its environmental range, exactly as Blyth pointed out so many years ago. Boundaries to its habitat are inevitably reached because the range of genetic adaptation has become exhausted. Although improvements may lie only a few base pairs away, they cannot be found. Only if the genetic system is again stirred up by external incidence can anything further take place.

External incidence appears to come in storms of rather short duration, the most recent very large storm being the one that occurred 65 million years ago, to which reference has already been made. Species seem to vary considerably in their sensitivities to genetic storms. Relatively insensitive species, those which largely exclude viruses, remain locked into a particular mode of existence. Such species are common among invertebrates, with insects, spiders, scorpions, and shrimps showing little or no evolution even over hundreds of millions of years. These are the so-called living fossils extending backward in time with essentially no change, in the case of some shrimps for as long as 500 million years. Other species, however, are highly sensitive to genetic invasion from outside. Such species face either extinction or immense change and fragmentation at a major genetic storm. Fragmentation comes from the imposition of a coarsely defined range of genetic possibilities, which after fragmentation are refined by the single base-pair adjustments discussed above. In effect, there is a genetic explosion, at first with the possibilities only broadly adapted to the environment, with the fine-scale adjustments subsequently taking place. It was the fine-scale changes that so greatly impressed Wallace and his contemporaries, and which do indeed fit the tenets of the neo-Darwinian theory. What the mathematics shows is that nineteenth-century biologists were correct so long

as they remained within the range of practical experience. Where the situation went wrong was in making a huge extrapolation from the safe ground of practical experience, and still more wrong in persisting with the erroneous extrapolation in more recent times, long after ample evidence was available to show that an incorrect guess had been made.

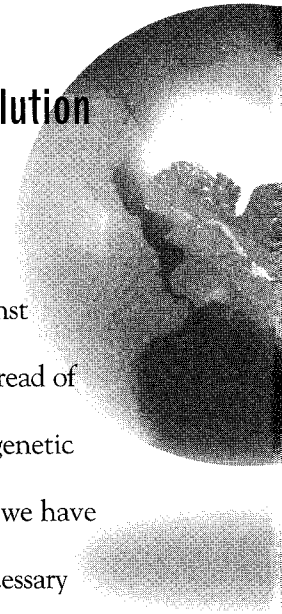
The reason why no connections are seen in the geological record between the orders of mammals is that the different orders are fragments from a genetic explosion, probably an explosion resulting from the immense storm of 65 million years ago. The explosion happened so quickly, producing creatures dissimilar to what had been there before, that the geological record failed to capture the explosion itself, only its products. In the mammalian case, the products are creatures of broadly similar type which emerged as fragments from the explosion, and which now constitute the different orders of mammals.

Likely enough a similar picture applies to an explosive fragmentation of an order into families of creatures, with such less violent convulsions arising from genetic storms of lesser magnitude, and with species repeatedly settling into fine-scale adaptations following every storm, whether the storm be large or small. A similar explosive concept was arrived at in the first half of the present century by the botanist J. C. Willis, but without a model to support it. Willis set out his case in a book *The Course of Evolution* (Cambridge University Press, 1940), which although rather repetitive contains an impressive array of facts. From botany rather than zoology, Willis arrives at the concept that in recent years has been call evolution by "punctuated equilibrium," a concept for which he gives references back to 1837, the same year which saw the pioneering work of Blyth. Naturalists in 1837 were very close to the truth, closer a cynic might say than they are today.

There is an interesting order of plants that I should mention, however briefly, before closing this chapter. The Scrophulariales have all the aspects of an explosion into genera. Their diversity is enormous. The order includes the tomato, potato, eggplant, chili pepper, tobacco, snapdragon, African violet, gloxinia and penstemon, bladderworts and magnificent ornamental trees such as the jacaranda and the white Indian cork tree. It is striking that the Scrophulars also date from the immense genetic storm of 65 million years ago.

Chapter 7

The Genetic Cost of Evolution



Selection cannot protect a species against deleterious mutations or promote the spread of favourable mutations without a cost in genetic deaths occurring. In the bisexual model we have studied from Chapter 3 forward, the necessary genetic deaths are born by an initially excessive population of juveniles, which besides standing up to accidental disasters imposed by the environment must also bear the cost of selection.

We took the juvenile population to be M, leading in each generation to a population N of adults who survive to reproductive age. For plants, invertebrate animals, fish, amphibians, most reptiles, and smaller mammals, M is so large compared to N that no great fraction of the available juveniles is required to die in order to maintain the integrity of a species with respect to deleterious mutations, or to permit sufficient advantageous mutations to penetrate a species to yield an effectively rapid rate of positive evolution. For the larger mammals and for many species of birds, however, M is not so large compared with N that the issue of genetic cost can be taken for granted. Typically in the latter cases, M might be about $5N$, corresponding to each mating pair producing an average of 10 offspring. It would not be unreasonable to suppose that 40 percent of juveniles fail to reach maturity for accidental nongenetic reasons, leaving $3N$ in these cases as the margin of juveniles on which selection can operate during a final reduction to an eventual population of N surviving adults.

We have seen repeatedly that $\exp -\lambda$ is a load factor imposed on every individual in order to prevent a continuing penetration of a species by deleterious mutations. With the deleterious mutations taken mostly to be recessive, that is, $h = 0$, λ is the average number of such mutations incurred in the replication of a single set of chromosomes, $\lambda \cong 0.3$ being a reasonable numerical estimate. If for simplicity of argument we also take the bulk of the recessive deleterious mutations to be lethal in homozygous individuals, $\exp -\lambda$ is the fraction of juveniles that must die to maintain the integrity of the species, about one in three, as we discussed in some detail in Chapter 5. Thus the need to maintain the integrity of the species reduces the margin of $3N$ juveniles to $2N$, leaving N who can be squeezed out in the promotion of positive evolution. Hence, we conclude for birds and larger mammals:

> That the number of juveniles who can be sacrificed to improve by selection the adaptation of a species to its environment is of the order of the surviving adult population. Neither birds nor larger mammals can evolve at a faster rate than is implied by this constraint, which evidently sets a maximum rate at which evolution can take place.

The human species is a critical example for testing this deduction, partly because the numbers taken above for M/N and for $\exp -\lambda$ are closely

applicable to the human case, and partly because human evolution over the past million years appears to have been very rapid. Has the measure of human evolution been consistent with the availability of dispensable juveniles one can ask? A similar question has relevance in other interesting situations, as, for instance, following one of the major genetic storms discussed in the preceding chapter. In the wake of such a storm, opportunities arise for rapid evolution along divergent lines: How rapid could such genetic explosions and fragmentations be? And on a lesser scale, a sudden change in the environment can throw a species out of a well-adapted condition: How quickly can positive evolution then recover adaptation? We considered the latter question previously for the peppered moth, but only for the change of a single gene. When many genes are involved how does the situation develop?

Just as we did for deleterious mutations, let all advantageous mutations have the same selective factor s, and let $s << 1$. Write Λ for the rate per gamete at which such mutations arise from changes to single base pairs on the DNA of a species. Then

$$\Lambda \approx 10^{-9} \text{ (Number of opportunities of improvement)} . \quad (7.1)$$

Here 10^{-9} per gamete is taken as the chance of a particular base pair happening to be miscopied into another explicitly stated pair. The interesting cases are those mentioned above, where the number of opportunities for improvement happen to be unusually large. But even if the opportunities were indeed remarkably large, say 10^6, we should still only have $\Lambda \approx 10^{-3}$, much smaller than $\lambda \cong 0.3$ for deleterious mutations. Λ must inevitably be small compared to λ, because the opportunities for damaging a complex and delicate system must always be much greater than the opportunities of improving it.

Let us first obtain the evolution rate for specified Λ, on the assumption that the constraint discussed above does not intervene. The rate of appearance of new advantageous mutations in a population of N individuals is $2N\Lambda$ per generation. Provided the constraint does not intervene, each mutation acts independently of the others, in which case the probability of each mutation penetrating and becoming fixed is the same as we calculated for a single gene in Chapter 4. Taking the mutations to be "semidominant," that is, taking $h = 1/2$, the results set out in Table 4.1 show that the fixing

probability is simply s, whence a fraction s of the $2\Lambda N$ advantageous mutations arising in each generation would become fixed. Should Λ be maintained for G generations the total number of advantageous mutations to become acquired by the species would therefore be $2\Lambda NsG$, and the improvement in the fitness of a typical individual (over the initial situation) would be

$$(1+s)^{2\Lambda Ns\,G} \cong \exp\left(2\Lambda Ns^2 G\right) \quad , \tag{7.2}$$

so that the improvement becomes considerable for

$$G > \left(2\Lambda Ns^2\right)^{-1} \quad . \tag{7.3}$$

Putting $\Lambda = 10^{-3}$ for a situation with a large number of possibilities of improvement, and taking $N = 10^6$, $s = 0.001$, (7.3) gives $G > 500$ generations. The generation length in the human case is about 20 years, so that the time scale for significant human improvement would be only ~10^4 years, an estimate that is consonant with fast evolution for our species. Such a gratifying result is contingent, however, on the existence of a large number of possibilities of improvement, and therefore on events creating such a multitude of possibilities, which is to say on a genetic storm adding to and shuffling the genes available to a species.

Returning now to the problem of whether the supply of juveniles is adequate to permit evolution at the rate implied by (7.2) and (7.3), the next step is to rework the analysis following (5.12), but with $s > 0$, $h = 1/2$ and replacing λ by Λ, the aim being to obtain the average number of advantageous mutations possessed by a typical individual. In place of (5.13) we now have

$$4\Lambda N\int_0^1 \mu(x)\,x\,dx \quad , \tag{7.4}$$

where the appropriate expression for $\mu(x)$ is

$$\mu(x) = 2\frac{\exp(2Nxs)}{x(1-x)} \bullet \frac{\int_x^1 \exp(-2Nzs)\,dz}{\int_{x_0}^1 \exp(-2Nzs)\,dz} \quad . \tag{7.5}$$

Again taking $2Ns >> 1$, we have

$$\mu(x) \cong \frac{2}{x}\exp\left(2Nsx_0\right) \cong \frac{2}{x} \tag{7.6}$$

for $x_0 = 1/2N$, $s << 1$. From (7.4) and (7.6) we see that the average number, μ say, of advantageous mutations possessed by an individual is

$$\mu = 8\Lambda N \quad . \tag{7.7}$$

With $N = 10^6$, say, and $\Lambda = 10^{-3}$ per gamete as the favourable mutation rate in a case where a very large number ~10^6 opportunities for improvement exist, we have $\mu = 8000$. Hence each individual possesses many favourable mutations in such a situation.

Selection takes place because of statistical scatter in the distribution of favourable mutations, those with $\mu + (\mu)^{1/2}$ mutations having a selective advantage

$$(1+s)^{2\sqrt{\mu}} \cong \exp\left(2\sqrt{\mu}\,s\right) \tag{7.8}$$

over individuals with $\mu - (\mu)^{1/2}$ mutations. The requirement that the supply of expendable juveniles be adequate to maintain the evolution rate is that the exponent of this exponential should not be greater than of order unity,

$$2\sqrt{\mu}\,s \leq \sim 1 \quad . \tag{7.9}$$

With (7.7) for μ we therefore require

$$32\Lambda Ns^2 \leq \sim 1 \quad . \tag{7.10}$$

This is in order that significant evolution may occur in $G = (27Ns^2)^{-1}$ generations. If the supply of juveniles is such that the upper limit imposed by (7.10) is attained, evolution can improve the fitness of a species by a factor e in only 16 generations, a very fast rate; indeed, a rate so fast that the limiting factor on the speed of evolution is seen to be the availability of advantageous mutations, not the genetic cost of evolution. Given sufficient availability, evolution can proceed at a rate which by any reasonable practical consideration is extremely rapid. The situation appears clear-cut and the circumstance that some geneticists have concluded otherwise raises something of a mystery, especially as a whole new school of mathematical biologists have used this issue to question the correctness of the Darwinian theory itself, preferring instead what has become known as evolution by neutral drift (for example, M. Kimura, *The Neutral Theory of Molecular Evolution,* Cambridge University Press, 1984). Quite apart from the impossibility of arriving at such proteins as histone-4 by random mutations—that is, random trials—the above considerations show that it is opportunity not the speed of evolution which is the problem for the Darwinian theory, the problem is the one emphasized already in Chapter 6, that opportunities are confined to those which can be reached by only single base-pair changes on the DNA.

On pages 26 and 30 of his book, Kimura states that for evolution proceeding at such a rate that one new gene with s = 0.01 is substituted throughout a species in 100 generations, the cost is so great that "no mammalian species could tolerate it, while for one new gene substituted every two generations each parent must leave $e^{15} \approx 3.27 \times 10^6$ offspring for one of the offspring to survive and reproduce." According to the above discussion, a fraction s of the $2\Lambda N$ advantageous mutations arising in each generation become fixed. Thus for one new gene to be substituted in two generations we require $2\Lambda Ns = 0.5$, in which case the genetic cost factor (7.8) is $\exp(8s)^{1/2}$. Since Kimura defines his selection coefficient to be half of our s, a value 0.01 in his statement corresponds here to $s = 0.02$, and $\exp(8s)^{1/2} \cong 2$. Such a genetic cost is just within the selective capacity of a

population with $2N$ juveniles available, the case considered above for birds and the larger mammals. For the substitution of one gene with $s = 0.02$ in two generations, only a few juveniles need be born for each surviving adult, an immense difference from the $\sim 3.27 \cdot 10^6$ juveniles which Kimura claims to be necessary. The discrepancy is indeed so enormous that it seemed necessary to attempt to trace its source.

The attempt proved a frustrating business. To start with, Kimura gives no explanations, only statements, and then only on pages 26 and 30 of his book. It seemed to me curious that, with 250 pages available, a clearer account of why the Darwinian theory was as devastatingly wrong as it is said to be shouldn't have been given. A carefully reasoned argument, at whatever length was necessary, would have been worthwhile in establishing so profound a result. In Fisher I also found nothing. In Sewell Wright's large treatise I found four pages (*op. cit.*, Vol. 3, pp. 434–437). What was this, I wondered, only four pages out of 2000 devoted to the disproof of Darwinism, and incomprehensible at that.

The concepts on which Kimura bases his statements seem to have first arisen in a paper of J.B.S. Haldane (*Journal of Genetics,* 1057, Vol. 55, pp. 511–524), a paper which I found just as curious as the more recent aspects of the story. Embedded in symbols, whose meanings were at first unclear, Haldane makes a statement that is both unequivocal and checkable:

> The unit of evolution, the substitution of one [form of gene] by another, if carried out by natural selection based on juvenile deaths, usually involves a number of deaths equal to about 10 or 20 times the number in a generation, and perhaps rarely being 100 times this number.

Let us examine this statement from two points of view. First, a correct point of view from which it can be seen to be untrue, and, second, a strange interpretation on which it seems to have been based. Write $x(t)$ for the frequency at time t of an advantageous mutation with initial frequency x_0. Provided the selection factor s is small compared to unity (as it is taken to be in Haldane's paper), it is irrelevant whether the ratios of the fitnesses of

$$(A, A) : (A, a) : (a, a)$$

are taken for the case $h = 1/2$ to be

$$1 + s : 1 + 1/2s : 1 \qquad (7.11)$$

or

$$1 : 1 - 1/2s : 1 - s \quad , \qquad (7.12)$$

since to the first order in s the form (7.11) can be changed to (7.12) simply by absorbing a factor $1 + s$ into the normalization coefficient α. For conformity with earlier calculations it would be better to use (7.11), but to permit easier comparison with Haldane and with Sewell Wright (*loc. cit.*), (7.12) will now be used. The normalization coefficient α for a population which remains constant from generation to generation is then determined by

$$\alpha\left[x^2 + 2x(1-x)\left(1-\tfrac{1}{2}s\right) + (1-x)^2(1-s)\right] = 1 \quad , \qquad (7.13)$$

that is,

$$\alpha = \frac{1}{1-s(1-x)} \quad , \qquad (7.14)$$

and the change of x from one generation to the next is given by

$$2\left(x + \frac{dx}{dt}\right) = \alpha\left[2x^2 + 2x(1-x)\left(1-\tfrac{1}{2}s\right)\right] \quad , \qquad (7.15)$$

that is,

$$\frac{dx}{dt} = \frac{1}{2}\,\frac{sx(1-x)}{1-s(1-x)} \quad , \qquad (7.16)$$

the unit of time being the generation interval.

In the absence of the selective factor s each juvenile of whatever genetic type would on the average have the same chance of surviving to reproductive age. But in the presence of the selective factor juveniles of type (A, A) have a chance increased by α of surviving to reproductive age, while heterozygotes (A, a) have a chance increased by $\alpha(1 - 1/2s)$ and homozygotes by $\alpha(1 - s)$. Hence the gain of survivors by type (A, A) is

$$Nx^2(\alpha - 1) = \frac{sNx^2(1-x)}{1-s(1-x)} \quad , \qquad (7.17)$$

the gain by heterozygotes (A, a) is

$$2Nx(1-x)\left[\alpha\left(1-\tfrac{1}{2}s\right)-1\right] = \frac{sNx(1-x)(1-2x)}{1-s(1-x)} \quad , \qquad (7.18)$$

and the gain by homozygotes (a, a) is

$$N(1-x)^2\left[\alpha\,(1-s)-1\right] = -\,\frac{sNx(1-x)^2}{1-s(1-x)} \quad . \qquad (7.19)$$

The sum of (7.17), (7.18), and (7.19) is of course zero, from which

$$\left|(7.17) + \tfrac{1}{2}(7.18)\right| = \left|\tfrac{1}{2}(7.18) + (7.19)\right| = \frac{1}{2}sN\frac{x(1-x)}{1-s(1-x)} \quad . \qquad (7.20)$$

While there is no absolute fiat as to how one must define the concept of "genetic deaths" quantitatively, it is sensible it seems to me to adopt (7.20), which then expresses the necessary condition that the gain of individuals due to A is equal to the loss of individuals due to a. The entire number of genetic deaths over all generations during which A becomes fixed in a species can

then be computed from

$$\int \left|\tfrac{1}{2}(7.18)+(7.19)\right| dt = \tfrac{1}{2}\int \frac{sNx(1-x)}{1-s(1-x)}\,dt$$

$$= N\int_{x_0}^{1} dx = N(1-x_0) < N \quad , \qquad (7.21)$$

in disagreement with the above quotation from Haldane. The result (7.21) assumes that the environment imposes a fixed number N on the population, forcing individuals with genetic variability to compete with each other. As a consequence of the competition, the frequency of A increases from x_0 to unity according to the selection equation (7.16). Since x_0 can be taken large enough for stochastic fluctuations to be ignored (i.e., $x_0 > s$), but with x_0 nevertheless small compared to unity, stochastic effects do not affect the result significantly. Such it seems to me is the standard concept of natural selection, whereby the constraint on the permissible number of individuals forces genetic change in a species. Hence, according to the standard concepts, the number of genetic deaths required to fix a gene (over $\sim s^{-1}$ generations) is close to the population number N, not a comparatively large multiple of N.

In practice, the assumption in the above calculation that N remains constant from generation to generation is unlikely to be strictly correct, because as a species improves its adaptation to the environment, competing species tend to be crowded out, thereby permitting N to increase. More strictly, N should be considered as a function of x. Before proceeding it is therefore necessary to consider whether the result (7.21) could be significantly changed by allowing N to increase with x. Suppose the original gene type a to sustain a population N_0, and let the population be $N_0 f(x)$ when the frequency of A has risen to x. In place of (7.13) we then have

$$\alpha f(x)\left[x^2+2x(1-x)(1-\tfrac{1}{2}s)+(1-x)^2(1-s)\right] = f\left(x+\frac{dx}{dt}\right) \quad , \qquad (7.22)$$

where on the left we have the production of offspring by the generation in which the gene frequency is x, and on the right we have the function f computed for the next generation. Thus

$$\alpha = \frac{1+d\ell n f/dt}{1-s(1-x)} \quad . \qquad (7.23)$$

In place of (7.15) we also have

$$2f\left(x+\frac{dx}{dt}\right)\left(x+\frac{dx}{dt}\right) = f(x)\alpha\left[2x^2+2x(1-x)\left(1-\frac{1}{2}s\right)\right] \quad , \qquad (7.24)$$

that is,

$$\left(1+\frac{d\ell n f}{dt}\right)\left(x+\frac{dx}{dt}\right) = \alpha\left[x-\frac{1}{2}sx(1-x)\right] \quad . \qquad (7.25)$$

Using (7.23), the factor $1 + d\ell nf/dt$ cancels in (7.25) and

$$\frac{dx}{dt} = \frac{1}{2}s\frac{x(1-x)}{1-s(1-x)} \quad , \qquad (7.26)$$

Since (7.26) is the same as (7.16), permitting the population to vary with x has no effect on the penetration of A.

We are now in a position to return to the paper of Haldane cited above. Suppose that the gene type A is deleterious up to time $t = t_0$, at which the frequency of A is $x_0 << 1$, the population number being N_0. At $t = t_0$ an environmental change occurs which causes A to become advantageous, so that thereafter the frequency x of A increases according to (7.26). It is also supposed that at time $t = t_0$ the population experiences a downward step from which it gradually recovers as A penetrates the species, until the original population N_0 is reestablished as x rises to unity. Such a model can be represented by choosing

$$f(x) = 1 - s(1-x) \tag{7.27}$$

with the population falling at time t_0 from population number N_0 to $N_0[1 - s(1 - x_0)] \cong N_0(1 - s)$. Thus the population when the frequency of A is x has the value

$$N_0 f(x) = N_0[1 - s(1-x)] \quad , \tag{7.28}$$

and the deficit of (7.28) below what the population would have been if there had been no environmental shift is

$$s N_0 (1-x) \quad . \tag{7.29}$$

The deficit (7.29) is for a single generation, while the cumulative deficit over the generations that elapse between the environmental change at $t = t_0$ and the recovery of the population to N_0 at $x = 1$ is given by

$$sN_0 \sum_{\text{generations}} (1-x) = sN_0 \int (1-x)\,dt$$

$$= 2sN_0 \int_{x_0}^{1} \frac{1-s(1-x)}{sx}\,dx$$

$$= N_0\left[-2(1-s)\ell n\, x_0 + 2s(1-x_0)\right] \quad , \tag{7.30}$$

where (7.26) has been used for dx/dt. Omitting the small terms in s, this is Haldane's result. Sewell Wright, on page 435 of his volume 3, includes the terms in s. Putting $x_0 = 10^{-6}$ as an example, the coefficient is about 14, and this is the source of the statement that natural selection for a favourable gene "usually involves a number of deaths equal to about 10 or 20 times the number in a generation. . . ." The deaths, however, have nothing to do with the cost of fixing a favourable mutation. The deaths have been caused by the environmental change, and are arbitrary at that, for if (7.27) were written

$$f(x) = 1 - S(1-x) \quad , \quad S \neq s \quad , \tag{7.31}$$

the number of deaths would be a factor S/s times (7.30). Hence (7.30) is an artifact of the particular environmental effect assumed in (7.27). One could argue with more sense that the penetration of a species by an advantageous gene permits the population to rise, say according to

$$f(x) = 1 + Sx \quad . \tag{7.32}$$

Then extra lives are lived, with a cumulative total during the fixing of the favourable gene

$$SN_0 \sum_{\text{generations}} x = SN_0 \int x\,dt$$

$$= 2SN_0 \int_{x_0}^{1} \frac{1-s(1-x)}{s(1-x)}\,dx \quad . \tag{7.33}$$

The integral here is logarithmically divergent at $x = 1$, because in the absence of stochastic effects the favourable gene never penetrates completely—as we saw from the outset in Chapter 1. Taking stochastics to fix the gene when x rises to $1 - \epsilon$, the lives gained number

$$2SN_0 \int_{x_0}^{1-\epsilon} \frac{1-s(1-x)}{s(1-x)} \cong 2\frac{S}{s}N_0\left[\frac{\ell n(1-x_0)}{\epsilon} - s(1-x_0)\right] \quad . \tag{7.34}$$

The situation is evidently so arbitrary as to be genetically irrelevant. What is genetically relevant is the result (7.21), representing the number of genetic deaths which occur in the fixing of a favourable gene against a fixed constraint on the population, and this is the way that the operation of natural selection is usually presented. Haldane's so-called cost principle is an illusion.

The reader may wonder if I could have misinterpreted the situation. I think not, for these reasons. As already mentioned, (7.30) is identical to the formula given by Sewell Wright, not just in the main term $-2\ell n x_0$ but also in the smaller terms involving s. Second, in the introductory remarks to his paper Haldane writes explicitly of environmental decline being caused by "pollution by smoke, a change of climate, the introduction of a new food source, predator, or pathogen, and above all migration to a new habitat." And third, if a logically sensible explanation of (7.30) existed, Haldane's paper would have been written more clearly than it was, Sewell Wright would have explained (7.30) instead of conjuring it like a rabbit out of a hat, and Kimura would not have based his book merely on the obscure remarks quoted above. He would surely have devoted a whole chapter at least to a careful analysis of the precise argument itself.

To end this chapter, let us see if we can at last understand the statement "each parent must leave $e^{15} \approx 3.27 \times 10^6$ offspring for one of the offspring to survive and reproduce." This statement was contingent on one new gene being substituted throughout a species in two generations.

Suppose at time $t = 0$ a set of n favourable mutations, all with the same selective factor s, have frequencies

$$x_0,\ x_1,\ x_2,\ \cdots\ x_r,\ \cdots\ ;x_{r+1} > x_r;\quad r=0,\ 1,\ \cdots\ n-1 \quad . \tag{7.35}$$

Using (7.26) for each of the genes, considered to become fixed independently of each other, the times $t_0, t_1, t_2, \ldots$ of fixing are determined by

$$t_r = \frac{2}{s}\int_{x_r}^{1}\frac{dz}{z(1-z)}\left(1-s\overline{1-z}\right) \cong \frac{2}{s}\int_{x_r}^{1}\left(\frac{1}{z}+\frac{1}{1-z}\right)dz \quad . \tag{7.36}$$

For one gene to become fixed every two generations we must have

$$t_r - t_{r+1} = 2\ , \quad r=0,\ 1,\ \cdots\ n-1 \quad . \tag{7.37}$$

From (7.36) and (7.37) it is easy to see that the values of $x_0, x_1, \ldots$ are narrowly spaced both at small x and when x is close to unity. The latter,

arising from the $1/1 - z$ term in the integrand of (7.36), can be omitted, however, because advantageous genes become quickly fixed by stochastic fluctuations when their frequencies approach unity. Hence, in practice, there would be no large number of genes with x values near unity. But those with x small must still be narrowly spaced, with x_r values determined by

$$t_r \equiv \frac{2}{s}\int_{x_r}^{1}\frac{dz}{z} \tag{7.38}$$

in the absence of stochastic effects, which can be neglected provided $x_r > \sim s$. From (7.37) and (7.38),

$$\frac{\Delta x_r}{x_r} = s, \quad \Delta x_r = x_{r+1} - x_r \quad . \tag{7.39}$$

Hence the total number of genes undergoing selection must be of order

$$\frac{1}{s}\int_{x_0}^{1}\frac{dx}{x} \approx -\frac{1}{s}\ell n\, x_0 \quad , \tag{7.40}$$

in order that one of them becomes fixed every two generations.

If now each favourable gene is accompanied by an environmental decline of the form (7.27), with x for most of the genes being $<< 1$, the total loss of fitness for the number (7.40) is

$$(1-s)^{-\frac{1}{s}\ell n\ x_0} \quad . \tag{7.41}$$

Kimura gives a slightly different index here, namely,

$$(1-s)^{\frac{1-\ell n\ x_0}{s}} \quad , \tag{7.42}$$

remarking that this change allows for the stochastic effects that were omitted above. For $s << 1$, (7.42) is simply

$$e^{-1}x_0 \quad . \tag{7.43}$$

In the discussion on page 26 of his book, Kimura first chooses $2(1 - \ell n\, x_0) = 29.6$ and then rounds $1 - \ell n\, x_0$ to 15, in which case (7.42) is $\exp -15 \approx 1 / (3.27 \times 10^6)$. Kimura interprets the result as follows:

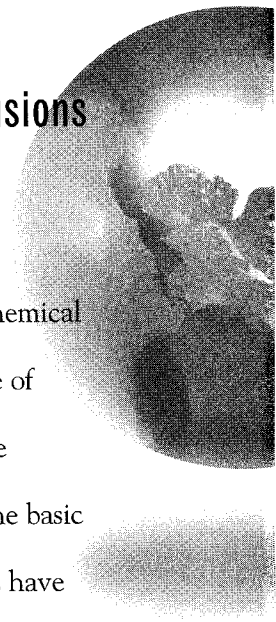
> This means that to maintain the same population number and still carry out mutant substitutions at the rate of one substitution every two [generations] . . . each parent must leave . . . $\approx 3.27 \times 10^6$ offspring for one of the offspring to survive and reproduce.

It actually means no such thing. It means if, on every occasion when a favourable mutant gene with selection factor s arises, the environment happens to worsen so that the population it can support drops discontinuously by the factor $1 - s$, then in order to force the mutations through to fixation at a rate of one every two generations, "each parent must leave $\approx 3.27 \times 10^6$ offspring for one of the offspring to survive and reproduce." The model is one in which mutations are forced through during an episode of continuing decline of the environment. It is no surprise that an immense production of juveniles should be needed to cope with an almost total collapse of the environment, involving of the order of a thousand downward steps in Kimura's example.

It is evident that these considerations have no relation at all to the usual situation in which the environment supports a more or less constant number of individuals, against which constraint favourable mutations are selected and unfavourable mutations checked. Not to put a fine point on it, the claims are illusions.

Chapter 8

Protein Phylogenies—More Illusions



Similar proteins involved in basic biochemical processes are found in an immense range of organisms, crossing the boundaries of the broadest taxonomic groupings even at the basic level of kingdoms. Usually such proteins have both similarities and differences in their amino acids, although in the special case of histone-4 there is scarcely any variation at all in a chain of 102 amino acids. A set of about twenty proteins

known as the cytochromes function together as electron-transfer agents. The third in the set as it is usually ordered, cytochrome-c, has been extensively examined (for details see M. O. Dayholt, National Biomedical Research Foundation, Washington, D.C.). Comparing the amino acid sequences in cytochrome-c from widely different organisms is not an entirely unambiguous procedure, however, because the amino acid chains can have different numbers of links. There are 104 links in mammals, 108 in insects, 108–110 in fungi, and 112 in plants. What is done when lengths differ is to use piecewise matching. The chains are considered to be broken into a small number of pieces in such a way as to achieve a maximum number of coincidences of the amino acids between what are taken to be the corresponding pieces. Where there are extra amino acids on one or other of the chains, these extra insertions are not counted in making a numerical estimate of the degree of matching. And because there is no unique length of chain, the matching is normalized by expressing the count in the form

$$100 \cdot \frac{\text{Number of coincidences found}}{\text{Number of links compared}} \quad . \tag{8.1}$$

Results for cytochrome-c would have been gratifying to older generations of taxonomists, for the greater the taxonomic diversity of the organisms compared, the larger (8.1) turns out to be. Grouping organisms in an alphabetic sequence as follows:

(a) bacteria
(b) fungi (baker's yeast, candida, debaryanyces)
(c) plants (wheat, sunflower, castor, sesame, mung bean)
(d) insects (hornworm moth, silkworm moth, fruitfly, screwfly)
(e) lamprey
(f) fish (tuna, bonito, carp)
(g) birds (penguin, chicken, turkey, duck)
(h) mammals (rabbit, dog, pig, cow, sheep, horse, monkey, human)

Per case we can denote comparisons within the same group by (*a*/*a*), (*b*/*b*), ... , and comparisons between different groups by (*a*/*b*), (*a*/*c*), (*b*/*c*), and so on. Except for (*b*/*b*), for which (8.1) can be as large as ~25, comparisons for

(*c*/*c*), (*d*/*d*), ... are ~8. Variations from group to group, on the other hand, gave the following remarkable results:

$$(a/b,\ c,\ d,\ e,\ f,\ g,\ h) \cong 65 \quad . \tag{8.2}$$

$$(b/c, d,\ e,\ f,\ g,\ h) \cong 45 \quad , \tag{8.3}$$

$$(c/d, e, f, g, h) \cong 38 \quad , \tag{8.4}$$

$$(d/e,\ f,\ g,\ h) \cong 25 \quad , \tag{8.5}$$

$$(e/f,\ g, h) \cong 17 \quad , \tag{8.6}$$

$$(f/g, h) \cong 17 \quad , \tag{8.7}$$

$$(g/h) \cong 12 \quad . \tag{8.8}$$

The number of links compared in the piecewise matching described above was usually about 105, so that there can be little difference for cytochrome-c whether we consider numbers to refer to actual counts or to the so-called distance given by (8.1). Some 35 amino acids are invariant across all the organisms, while ~65 are variable in the largest distance from bacteria to the other organisms, with lesser distances being found the greater the taxonomic similarity between the organisms. The invariant 35 amino acids must be precisely defined in order that cytochrome-c can perform its enzymatic function. The remaining ~65 amino acids are in some degree variable. But it seems highly unlikely that the latter can be changed without selective advantages or disadvantages arising, since it would be most peculiar to have 35 amino acids obligatory and the remainder free—free to within a selective margin of, say, 1 part in 10^6, as they would need to be in order to be treated as selectively neutral, which is the assumption that has been made by investigators who have used values of (8.1) to construct a so-called phylogenetic tree, a tree which purports to demonstrate the course of evolution going all the way from a common ancestral cell to present-day species. Rather does it seem that, with ~1/3 of the amino acid links mandatory in the cytochrome-c chain, the other ~2/3 of the links will be selective

according to the particular function of an organism, with (8.2) to (8.8) interpreted in terms of the functions of the organisms in question.

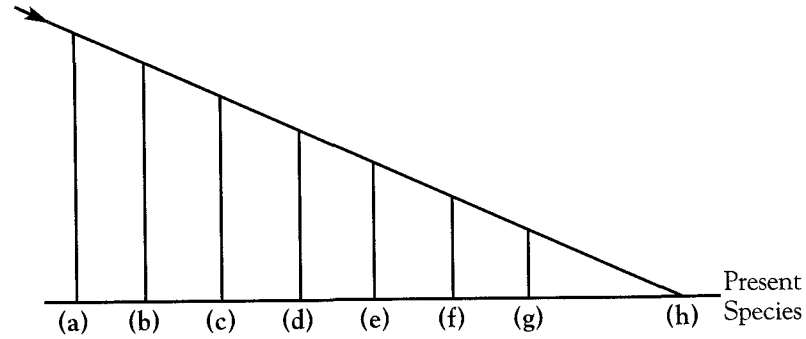
Bacteria are so different in function from the other organisms that all ~65 potentially variable amino acids in the cytochrome-c molecule are optimized differently for bacteria from all the others. Of the ~65 possible variations, ~25 are optimized in the same way by all the others in (*b*), (*c*), ... (*h*). Thus fungi, plants, and animals utilize the ~40 variations to optimum advantage in different ways. All animals make optimum use of ~15 of these possibilities in the same way, but insects as representatives of the invertebrates employ the remaining ~25 optimally in different ways to vertebrates. Among all vertebrates about 8 amino acids are optimized in the same way, leaving ~17 of the ~25 to be distributed according to the kind of vertebrate, with the lamprey, bony fish and birds + mammals employing the ~17 still adjustable amino acids differently. Among birds + mammals, ~5 of the ~17 are optimized commonly, leaving ~12 to take different forms in these two comparatively close cases.

All this is not to say that the various categories (*a*), (*b*), ... (*h*), or some of them, did not have evolutionary connections, but that similarities and dissimilarities of function are alone sufficient to explain the observed amino acid differences. The situation is simply that plants, fungi, and animals optimize differently. Among animals, the vertebrates and invertebrates optimize differently. Among vertebrates, amphibians optimize differently from animals that live either wholly on the land or in the sea. Among vertebrates living on the land, those that are reptiles optimize differently from those that are mammals, while, finally, among any particular one of the categories (*a*), (*b*), ... (*h*), there is fine-tuning according to the detailed differences of function that exist within each category. The essential point is that similarities and dissimilarities of function, provided they introduce selective factors $s > 10^{-4}$ to 10^{-5} take control of the situation, determining the identities of the changeable amino acids in a cytochrome-c chain. Evolution there may have been, but memories of evolution are masked by selective necessities.

Phylogenetic trees for proteins such as cytochrome-c are invalid unless the variable amino acids used for constructing the trees drift neutrally to within 10^{-6} to 10^{-5} in the selection factor for mammals and to even finer margins for species with very large populations—invertebrates and plants. This would imply that most amino acids of enzymic chains do not matter, an exceedingly unlikely supposition in view of the mandatory character of the rest of the amino acids. To argue that while a fraction of amino acid sites are crucial, the

fraction ranging from about 1/3 for cytochrome-c essentially to 1 for histone-4, to the extent that they cannot be varied at all, while the rest can be varied freely without selective advantage or penalty appears quite unreasonable.

Besides which, there are three further objections, one a *reductio ad absurdum*, another a flaw of logic, and the third a disproof by positive fact, that rule protein phylogenies so far out of court that one must wonder at the state of confusion which led to them ever being considered at all. Suppose we accept that ~65 amino acids of cytochrome-c can drift without selective control. Then (8.2) to (8.8) lead inferentially to the following schematic evolutionary picture in which time is considered to advance in the sense shown by the arrow, with evolution causing branchings to occur so as to lead at the present moment to the groups (*a*), (*b*), ... (*g*), (*h*).



The ordering of the branchings in the sketch, taken with the hypothesis of random drift for ~65 of the amino acids of cytochrome-c, requires that (*a*), the first group to peel away from the others, shall show the greatest number of amino acid differences from the other groups. Omitting (*a*), (*b*) will then show the greatest number of differences, and so on, in the same order as the decreasing numbers on the right-hand sides of (8.2) to (8.8).

What this view of events does not explain, however, is why the differences between (*a*) and (*b*), (*c*), ... (*h*) should all be essentially the same, why the differences between (*b*) and (*c*), (*d*), ... (*h*) should all be essentially the same, and so on. Additionally for this, we would have to assume that random drift of the variable amino acids has occurred at the same absolute time rate for all the species of (*b*), (*c*), ... (*h*). Then it will not matter which species from (*b*), (*c*), ... (*h*) we choose, its total of amino acid difference from

(*a*) will be the same to within statistical fluctuations. Similarly for the difference between (*b*) and any species taken from (*c*), (*d*), ... (*h*). And so on, through the sequence (8.2) to (8.8). But the trouble for this interpretation of (8.2) to (8.8) is that mutations occur with respect to generations, and generations do not relate uniquely to time. Among mammals there is more than a tenfold difference of generation interval between mice and rabbits on the one hand and horses and shrimp on the other. Variations of generation length can be as much as a hundredfold among insects, while yeast and some other fungi have generation lengths which are minute compared with most other species. Yet the constant differences in (8.2) to (8.8) hold good to margins of as little as 10 percent for the larger numbers and to about 20 percent for the smaller numbers, an impossibility for even twofold or threefold variations in generation intervals, which are common. This is a *reductio ad absurdum* so evident that protein phylogenies should surely have been instantly dismissed on this ground alone.

Possibly worse still, protein phylogenies lack proper causality. Mutations between branchings are assumed to have stayed the way they were at the moment they occurred. A mutation that occurred, for example, during the time intervals between the branchings of (*c*) and (*d*), is assumed to be possessed by all species in (*d*), (*e*), ... (*h*). But the amino acid in question may have changed again for some of the species in (*d*), (*e*), ... (*h*), changing in different ways for different species. When numbers of mutations are few compared to the number of changeable amino acids, this objection would not be serious, it would be a second-order effect. But for cytochrome-c, where essentially all amino acids that are changeable have been changed in one species or another, multiple mutation at the same amino acid site are not necessarily of second order.

The only data available for constructing a phylogenetic tree are of course the variations found in present-day species. Even if there has been a tree of the assumed type, present-day data are insufficient to reconstruct it. This is well recognized, and what is usually done in order to obtain a unique tree is to choose the branches and the numbers of mutations associated with them by a minimum criterion of some kind. What does not seem to be so well recognized is that because of repeated mutations the method is invalid when used, as in the case of cytochrome-c, over long time intervals. The original situation, if it existed, is irrecoverable, just as a system of differential equations is not soluble when the boundary conditions are incomplete.

The third objection is straightforwardly practical. Hemoglobin consists of four copies of the hem- group of about a hundred atoms, featuring iron prominently, held in a tetrahedral-like structure by four chains of amino acids. Of the four chains in mammals, two consist of α-hemoglobin with 141 amino acids and two of β-hemoglobin with 146 amino acids. Both the α and β forms have existed throughout the evolution of mammals and, if a phylogenetic tree could validly be constructed from the amino acid chains of proteins, one should evidently obtain an indirect tree from the α and β forms. With the same tree, and with mutations occurring at an assumed constant rate with respect to time, amino acid differences between one mammal and another should be the same to within a normalization factor of order unity for α-hemoglobin as for β-hemoglobin.

Table 8.1
Matrix Showing Differences Between Mammalian Species for Hemoglobins α and β: (α / β)

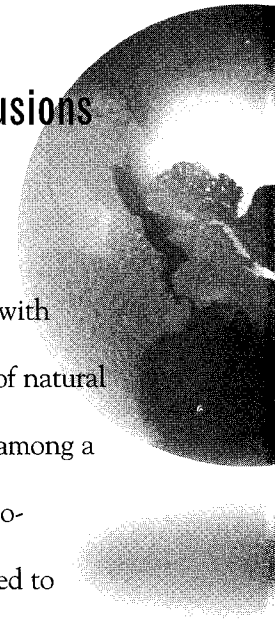
	Human	Mouse	Rabbit	Dog	Horse	Cow
Human	X	18 / 27	25 / 14	23 / 15	18 / 25	17 / 25
Mouse	X	X	27 / 28	25 / 30	24 / 36	19 / 39
Rabbit	X	X	X	28 / 31	25 / 25	25 / 30
Dog	X	X	X	X	27 / 30	28 / 28
Horse	X	X	X	X	X	18 / 30

But there is no normalization factor of order unity that brings the numbers shown in the table on page 133 into consonance with each other. These numbers are a direct and obvious disproof of the whole concept of protein phylogenics.

Although phylogenies using proteins have been mainly featured and emphasized in evolutionary literature, phylogenies using DNA are increasingly being investigated. Such phylogenies are open to just the same criticisms If they include base pairs that can be of selective relevance. But variations contingent on the redundancy of the genetic code should genuinely satisfy the postulate of neutrality and so be a satisfactory source of evolutionary data. Redundant DNA, not giving rise to expressed proteins, may also be expected to drift neutrally, although phylogenies extending over long time intervals are not secure even for redundant DNA, since DNA that is presently redundant may not always have been unused.

Chapter 9

Summary and Conclusions



The present essay has been concerned with evolution in the small, with the effects of natural selection on point mutations occurring among a fixed aggregate of genes, the classical neo-Darwinian situation. When genes are tied to each other, as they are when reproduction from generation to generation follows an asexual binary fission model or a budding model, there can be no positive evolution. Rarer

advantageous mutations are swamped by more frequent deleterious mutations. The best that natural selection can do subject to a specified environment is the hold the deleterious mutations in check. When the environment is not fixed there is a slow genetic erosion, however, which natural selection cannot prevent. To avoid this slow erosion, organisms like bacteria that propagate asexually must spend lengthy periods in deep hibernation, taking up an inactive phase which may involve the production of spores.

Eucaryotic organisms typically possess sexual cycles at primitive levels and propagate sexually at higher levels. Together with the phenomenon of crossover, sexual cycles and sexual propagation uncouple mutations on different genes. Provided two genes are not sited close together on the same chromosome, mutations occurring to them can be regarded as becoming uncoupled in a few tens of generations. Even genes sited adjacently on the same chromosome separate in a few thousand generations. This is still much shorter than major evolutionary time scales. The important effect of uncoupling mutations is that natural selection can then promote advantageous changes as well as keeping the more frequent deleterious mutations in check, a desirable result tempered, however, by two considerations. With mutations uncoupled, natural selection cannot turn back deleterious mutations if they are very small, and over a long time a large number of small disadvantages escalate to a serious handicap. This long-term inability of natural selection to preserve the integrity of genetic material sets a limit to its useful life, a limit estimated in Chapter 5 to be some 10^6 to 10^7 generations. Over long periods, a species must either acquire new undamaged genetic material or decline occurs. Redundant DNA may be an accumulation of genetic material that exceeded this limit at times in the past and which has now become discarded.

The second consideration of fundamental importance in a sexual model is that half the genes of two parents are discarded in a generally random way at the birth of every offspring, a roll of the dice situation that inevitably leads to stochastic effects which cause most small advantageous mutations to be lost. This loss, perhaps surprisingly, does not prove a particularly serious difficulty for large populations and for mutations that do not involve changing more than one base pair on the DNA of a gene. Subject to this crucial condition, an advantageous mutation can be discovered and rediscovered often enough for it eventually to run the gauntlet of stochastics and for it to penetrate and become fixed in a species.

For populations exceeding 10^6 individuals among whom mating occurs at random, the limitation on positive evolution is set by opportunity, not by the cost of selection as some investigators have maintained. Opportunity consists of improved adaptations to an environment that can be achieved by only a single base-pair change on the DNA. Should two or more base-pair changes be required before an advantage can occur, even large populations are unlikely to discover it. Thus opportunity exists only when genetic material is already very close to an improved state. Examples arise in fluctuating environments, because a form of gene that is an advantage in one environment can become a disadvantage in another. An environmental change can sometimes make it desirable to knock a working gene out of action, and a single sensitive base-pair change may be sufficient for this, thereby creating an opportunity of recovery were the environment to return to its original state. An environmental oscillation between light and dark trees for the peppered moth was the example considered in Chapter 6.

The ability of species to adapt by changing one base pair at a time on any gene, and to do so with comparative rapidity if selective advantages are reasonably large, explains the fine details of the matching of many species to their environment. It was from the careful observation of such matchings by naturalists in the mid-nineteenth century that the Darwinian theory arose. Because the observations were made with extreme care, it was highly probable that immediate inferences drawn from them would prove to be correct, as the work of Chapters 3 to 6 shows to be the case. What was in no way guaranteed by the evidence, however, was that evolutionary inferences correctly made in the small for species and their varieties could be extrapolated to broader taxonomic categories, to kingdoms, divisions, classes, and orders. Yet this is what the Darwinian theory did, and it was by going far outside its guaranteed range of validity that the theory ran into controversies and difficulties which have never been cleared up over more than a century.

While it is a good plan to attempt to apply new ideas as widely as possible, there were several reasons for misgivings even at the outset to which more attention should have been paid. The argument given a quarter of a century earlier by Edward Blyth, an argument which really proved that species cannot adapt outside fairly narrow limits was side-stepped instead of being answered. There was also the difficulty that the fossil record did not support Darwin's concept of major changes, as for instance from reptiles to

mammals, being achieved by very many small steps. Interesting discoveries were indeed made in the fossil record, but they only represented adaptations of established orders, not the larger connections which should have been there if the theory were fully correct. The presentation of discoveries to the public was heavily biased to emphasize the pros and hide the cons, a process much aided by the founding in 1869 of the weekly science magazine *Nature*, a magazine which has always seen the presentation of the Darwinian theory in the most favourable light as a primary objective.

The problem of speciation was necessarily difficult in the nineteenth century. What is it that permits a group of individuals, which commonly we describe as forming a species, to mate successfully generation after generation, while a somewhat wider group of still-similar individuals cannot do so? We know today that the two chromosome sets denoted in Chapter 2 by P and M, which an individual obtains from its male and female parents respectively, must be sufficiently alike for $(2P, 2M)$ to be arranged into quartets, $(2p, 2m)$, that can be matched with sufficient accuracy for crossover followed by successive cell divisions to take place. If P differs by more than a small amount from M, the complex process of meiosis goes wrong. There is the very major difficulty for evolution in the large that the chromosomes of widely separated taxonomic groups are very different—reptiles are very different from mammals. So how did the chromosome structure of reptiles change into that of mammals? If we say by internal mutations, many small steps would be needed, since a large change of structure occurring in one step to one individual would be sterile, because it would be unmatched in individuals of the opposite sex. Indeed, any such large change would have small probability in the first place, and the further chance of a contemporary member of the opposite sex possessing just the same internally generated large change would be much smaller still. The consequent need to multiply minuscule probabilities rules out large spontaneous changes of chromosome structure, leaving only the alternative of very many small changes. Many changes should be traceable in the fossil record, which they have not been.

The concept discussed in Chapter 6 of an externally incident genetic storm overcomes this difficulty, because both the chromosome sets P and M are exposed to the same external source of change. Both males and females are acted upon in the same way, and although for any particular mating couple the chance of P and M being altered by external attack in an advantageous way may be small, the small chance is not squared. Given a

sufficient number of couples in a large enough population and an advantageous change will happen sooner or later, especially as genetic storms probably continue for $\sim 10^5$ generations. Hence the total number of couples exposed to change is $\sim 10^5 N$, a large number, permitting even very unlikely alterations to P and M to happen, should they lead to a viable organism. Large changes to P and M separate the offspring of a mating couple immediately from their ancestral stock, and if several such changes occur, the ancestral stock becomes fragmented into nonmiscible branches, branches sterile with respect to each other. Only organisms in the same branch can mate successfully so that the fragmentation is a one-way process. Having happened, there is no turning back. The same process operating on a much less drastic scale than fragmentations into classes and orders can ultimately explain the appearance of species. This picture is strongly supported by the mathematical discussions of previous chapters, which showed that changes involving a multiplicity of base pairs can never be discovered by internal mutation. Changes even much smaller than those just discussed cannot arise spontaneously.

Since we are biological creatures, it might be expected that physical things would exist to serve biological things. Yet the odd thing about present-day society is that its physical activities appear purposive and its biological activities only weakly so. Few among us have any real idea of what we are up to, biological speaking, except to say that we work at a job to "earn a living," or that we are "bringing up a family," or in the case of the young that we are preparing to find a job to earn a living, or to find a partner to bring up a family. Frankly speaking now, just the same protestation could in principle be given by a cow munching in a field. Migratory birds moving with the seasons, often with great inherent skill and seemingly with considerable knowledge of geography, could be said to display a superior sense of purpose, which is perhaps why so many humans are fascinated by the practice of bird-watching.

What is evidently missing from present-day society is biological knowledge of the same high quality as the physical knowledge which at present guides our activities, but which by itself can only be aimless. The major reason, I believe, why biological knowledge has so far had little impact on society is that it has no proper foundation. The mistaken extrapolation from evolution in the small to evolution in the large that followed the Darwinian theory of 1859 led society into a bog which has only grown deeper with the passing years.

Just as our physical knowledge is expressible in mathematical form, so must biological knowledge if it is ever to have a real impact on society. Here I can only give a few hints of what might be possible. It is against the constraint of the population number N sustainable by the environment that selection and evolution take place. Humans differ from all other animals in that N depends to a major degree on knowledge. That possessed by Stone Age humans was sufficient to maintain a total population estimated to have been about 10^6. Modern knowledge, on the other hand, could probably sustain a world population of 10^{10}, an immense difference. While the dominant component of knowledge to this point has been how to grow food under controlled conditions and how to manufacture articles with concomitant access to large sources of energy, the psychological attitude of humans to themselves is beginning to affect "knowledge" and so to become a part of our environment.

Psychological attitudes have led in the present century to a new and potentially important development in Western Europe, namely to N taking a value appreciably less than the population could have been if numbers had been pressed to their logistic limits. A consequence is that the juvenile population M is no longer much larger than N, a situation which led quickly to the modern concept of a compassionate society. If this concept is not to be a temporary notion, it is essential that N be prevented from rising anywhere near its logistic limit. One can say that the potential for humans to control their environment is determined by the extent to which N is kept below the logistic limit, $\bar{N}$ say. For N appreciably less than $\bar{N}$ the potential for compassion is great, for N approaching $\bar{N}$ compassion becomes difficult, while for $N = \bar{N}$ no compassion at all is possible, since $N = \bar{N}$ implies a return to the raw biological conditions that obtain for most species, and which have obtained for humans throughout most of their history.

The circumstance that at the birth of every offspring a half of its two parents' genes are discarded creates the possibility that biological knowledge can be at least as crucial to our environment in the future as physical knowledge has been in the past. At present and throughout history, the discarding process happens essentially at random. But let random discarding be replaced by controlled discarding and everything would be changed. The need for juveniles to be perpetually sacrificed in order to maintain the genetic integrity of our species would disappear. The discarding of genes at random in the production of gametes must continue of course, but the choice

of which gametes fertilize to produce offspring need not be at random. Only gametes with fewer than the average number of genetic defects need be fertilized, so that only offspring with less than the average number of defects are born. None would then need to be sacrificed. Indeed, by exercising choice over which gametes fertilize and which do not, all present defects could be eliminated from the human species in only a few generations. Human abilities show a spread nowadays between those individuals who are abnormally good at some activity, whether physical or mental, and those who are abnormally bad. The effect over a number of generations of removing all defects would be to put everyone in the abnormally good category, and to do so for every activity. There would be a complete removal of the hitherto sustained misery of those who are born handicapped, the latter being a necessary consequence of the present situation in which bad genetic choices are as likely as good choices, with a weeding out of the bad being left to the sufferings of unfortunate individuals.

Granted that the whole genetic complement of the human species is made to work in everybody at more or less maximum efficiency, what then? Would we wish thereafter to become genetically fixed, a complex example of a living fossil? Presumably not. But the natural alternative of submitting ourselves to random genetic explosion in the next genetic storm to invade the Earth does not appear attractive either. Rather would our instincts be to shield ourselves in some way or other from the effects of serious disease, let alone from the full consequences of a major genetic storm. The remaining alternative for change is to splice new genes into our DNA in a controlled way, a possibility that modern genetic engineering brings into range. To many, such a possibility arouses distraught visions of Frankenstein's monster. There would certainly be no shortage of opponents to it. In the respect that nobody in authority today seems to have much grip on what they are doing, I would share this fear. But not logically. If it were clearly demonstrable that one could acquire a new gene with little fuss and bother that provided immunity against the common cold, I for one would be glad to have it. Cancer may possibly arise from an immunity problem, and if a new gene providing immunity against cancer were available most people I suspect would be only too glad to acquire it. The problem lies not in the aim but in our present-day lack of knowledge, just as it did for centuries in the physical sciences.

We saw in Chapter 5 that the amount of expressed DNA in mammals is very likely limited by the pressure of deleterious mutations, by the factor

exp $-\lambda$. With this pressure removed in humans, through control over choices of gametes, the total of expressed DNA could be increased without penalty, thereby opening the road to evolutionary attainments that otherwise would be unreachable. Such a development would evidently be a very long-term affair. Yet to so questing an animal as the human, it is important to conceive that the road to an eventually much superior status is not irrevocably blocked, as it would appear to be so long as random choices of gametes continue to rule the day.

Let population being
With many possible
A, all taken to have
selective factor $s < 0$,
per single set of chromosomes
(i.e. per somite) the total number of mutations
arising over a long time interval of T years
in a fixed population of N individuals is
$2\lambda NT$. An individual born within the
interval has a chance given by the time
average of (6.1) of having
respect to any one of the $2\lambda NT$ mutations

$$\frac{1}{T}\int_0^T x^2\,dt \int \phi(x,t)\,dx, \qquad (6.2)$$

sampled at time t
deleterious mutations
the same advantage
occurring at a rate
chromosomes per generation
total number of mutations
time interval of T years
of N individuals is
born within the
given by the time
homozygous with
the $2\lambda NT$ mutations

Mathematics of Evolution

"So, I said, let's calculate. . . ."

Cosmologist Fred Hoyle applies his prodigious mathematical talent to the problem of evolution. Professor Hoyle has had a distinguished career as a theoretical physicist, writer and researcher. At the University of Cambridge, he was a lecturer in mathematics before he was made Plumian professor of astronomy and experimental philosophy in 1958. He founded and was the first director of the Cambridge Institute of Theoretical Astronomy in 1967, was named an associate member of the American National Academy of Sciences in 1969, and has been an honorary professorial fellow at University College, Cardiff, since 1976. He has been awarded many honors and was knighted in 1972. Sir Fred Hoyle has shown himself to be a gifted scientist and writer who is willing to address fundamental problems and to challenge established ideas in science.

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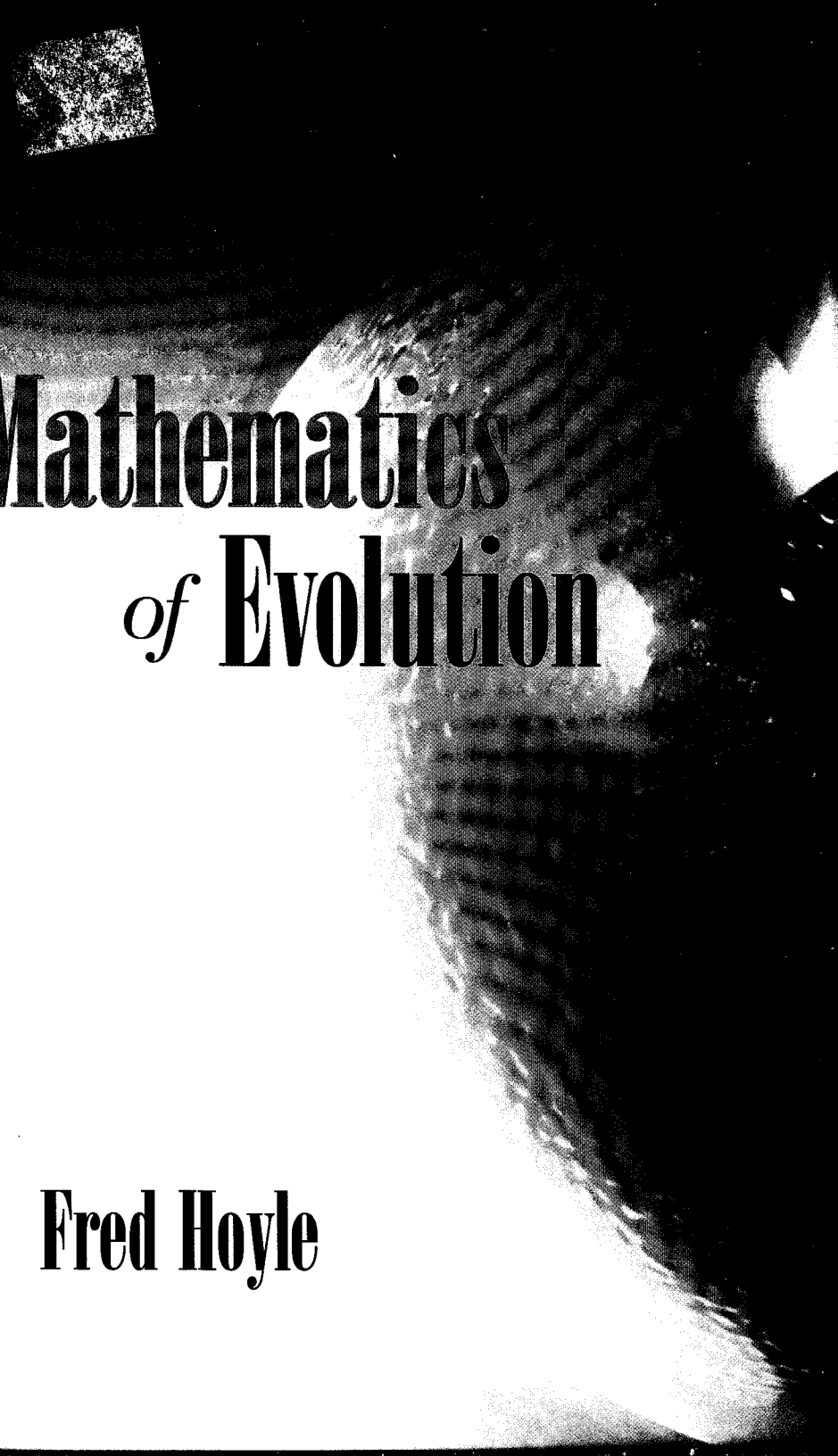
Mathematics of Evolution
Fred Hoyle



Mathematics of Evolution

Fred Hoyle