The Marriage of Mathematics and Biology

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For most of my life as a scientist, I have been trying to apply mathematical reasoning to biology. It seems that my efforts have been sufficiently successful to lead the Inamori Foundation to honour me by the award of the Kyoto Prize. I am deeply grateful for this honour: no scientist could fail to be moved by this unique recognition. The award has an additional consequence which I welcome: in asking me to deliver this address, the Foundation has forced me to examine my life in science. In particular, how did my upbringing prepare me, and how did it prepare me to apply mathematics to biology?

Mathematics was not applied seriously to biology before the 1920s. Its first important successes were in the field of evolutionary biology. Darwin was supreme in conceiving general biological laws—in particular, the theory of evolution by natural selection—and in applying them to the details of natural history. But he was no mathematician. Mathematics became necessary after the rediscovery of Mendel's laws in 1900, and the growth of the new science of genetics. However odd it may seem today, Mendelism was at first seen as the enemy of Darwinism: it held that new forms—even new species—arose suddenly by mutation, whereas the Darwinians saw evolution as the result of the natural selection of a multitude of minute variations. The result was a fierce debate, in which neither side understood what the other was saying. It needed mathematical analysis, notably by the great triumvirate of R. A. Fisher, J. B. S. Haldane and Sewall Wright, to marry Mendel and Darwin, a marriage which continues to be the mainstay of evolutionary thinking.

My own interest in biology goes back a long way. I was born in London, and lived there until I was eight years old, when my father, a surgeon, died, and I went to live in the country with my mother and sister. In London, I was already fascinated by animals, and demanded visits to the Zoo, and in particular to the Natural History Museum, where I learnt many of the dinosaurs by name. When we moved to the country, I put out food for the birds in the winter, and identified for myself some dozen species. It was a great excitement when, after a year, I was given a small bird book by a discerning aunt, and found the names of the species I had identified. I had got the identifications right, except that I did not realize that the black bird with the yellow bill, and the dark brown bird of similar shape, were the male and female of the same species. In the summer I collected butterflies, and I kept tadpoles and other pond animals—I still remember my horror when I put the carnivorous larva of the beetle Ditiscus into a tank as a companion for my tadpoles.

This love of natural history has stayed with me. I still watch birds, and love identifying wild flowers. I have also become an enthusiastic gardener. Why this interest? It was certainly not adult encouragement: indeed, I regret that there was no-one around who could help me, or broaden my interests. All I can say is that a passion for natural history arises in some children, for unknown reasons, and often lasts for life. It can be an invaluable aid to an evolutionary biologist. Darwin was a naturalist, and tells us that he was first led to the idea of evolution by his observations on the finches and tortoises of the Galapagos Islands.

The second thread in my scientific career has been a love of mathematics, and here I did get adult encouragement. I spent the years from 8 to 18 at boys' boarding schools—an experience that I loathed. The core of the education was the classics—Latin and Greek. I have no gift for languages, and was therefore regarded as a rather stupid boy, until it was discovered that I was quite good at maths. In fact, my ability is limited: I am good at geometry, but my skill at manipulating symbols is very limited. Fortunately, at Eton (my 'public' school, from age 13-18) geometry was taken seriously, and from the age of 15 I was taught mathematics in a small group of 5-6 boys. The teaching was brilliant, and I will always be grateful to the masters who taught me. The core of the training consisted of a set of ten problems which we had to solve, or attempt to solve, each week. I spent many hours each week struggling with these problems. This taught me something that many science students (particulary, I fear, in biology) never learn: if you are faced with a question to which you cannot at once see the answer, it may be possible to find the answer by thinking about it. I love problem-solving. Even today, when I have plenty of real scientific questions to think about, I waste time solving the mathematical puzzles in the newspaper we take on Sundays.

The only science I learnt at school was Newtonian mechanics, which was treated as a branch of mathematics: no other physics, and no chemistry or biology. But I learnt quite a lot of science on my own: for example, I acquired a fair understanding of special relativity and elementary quantum theory, and read a lot about evolution, including Darwin's Origin of Species. In 1948, I went to Cambridge to read 'mechanical sciences', which meant engineering. It had never occurred to me that one could earn one's living as a biologist—after all, Darwin didn't. I already knew that I would never make a proper mathematician. Engineering seemed a chance to use my mathematical ability. This proved to be a lucky choice. An engineering training teaches one to make mathematical models of the world. It also taught me that a model cannot be the whole truth: to be useful it must be simple, and the whole truth is never simple. For example, in those days aeroplanes were designed on the assumption that air is an incompressible fluid—a manifest falsehood. But so long as one flies well below the speed of sound, the assumption of incompressiblity gives predictions that are close to the truth. In biology, models always have to be simplifications, because real organisms are immensely complicated. The trick is to make the right simplifications.

In normal times, I would probably have switched from engineering to biology while at Cambridge. But times were not normal. The war broke out, and a half-trained engineer had no choice but to complete his training and enter industry. I became an aircraft 'stressman', responsible for ensuring that the aircraft structure did not break under the loads imposed. I worked at Miles Aircraft, a company that built training aircraft. I worked very hard, but I do not think I made any useful contribution to Britain's war effort, although aeroplanes I worked on were widely used after the war. Finally, in 1947, I left the aircraft industry and returned to university to study biology.

Before describing my life as a biologist, I want to say a few words about how these two streams—biology and mathematics—came together. The key lies in my interest in evolution, which dates back to my schooldays. My interest was in part philosophical. How did human beings come to be as they are? Is it possible to explain the complexity of the living world without assuming the existence of an intelligent creator? My family accepted Christianity without thinking seriously about it. I do not know why I started to ask questions about it. I was certainly stimulated by some of the books I read—but why did I read those books? The questions I was asking concerned politics as well as philosophy. I suspect that the stimulus to ask questions arose because, increasingly, I came to dislike the culture and assumptions of the school, Eton, that I attended, which seemed to me at once mindless and arrogant.

Whether or not that is true, from the age of 15 I started reading widely in politics, philosophy and science. There was little science fiction in those days, but I read what I could find—notably H. G. Wells. I want to mention two books in particular that influenced me profoundly. The first is a science fiction book, Last and First Men, by Olaf Stapledon, first published in 1930. It is a history of the next 2000 million years. Its basic theme is that humans are unable to build a stable civilization until they change their own natures. Successive civilizations rise, and collapse. In our immediate future, Stapledon describes—in 1930!—the threat of atomic war, and the collapse of civilization caused by the exhaustion of oil supplies. Finally, one civilization sets out to transform human nature by genetic engineering. To do so, they construct giant artificial brains—made of neurones, not transistors, but Stapledon could not get everything right. Today, I do not think I accept Stapledon's major thesis, that a stable society requires that human nature be changed genetically, or at least I hope it is wrong. But he did introduce me to the importance of genetics and evolution.

The second book is J. B. S. Haldane's Possible Worlds. I remember what led me to read it. Haldane had been at Eton. He was the one person my teachers most hated—he was a socialist and an atheist, and they saw him as a traitor. I remember thinking that anyone they hated that much could not be all bad. To their credit, however, one of his books was in the school library. It is a collection of essays about biology, philosophy and religion. I cannot resist describing the 'possible world' of the title essay. There is a race of intelligent barnacles. They classify objects into two classes: 'real' objects that they can reach with their arms, and 'imaginary' objects that they can see but not reach. Occasionally an imaginary object will, for one barnacle, turn into a real one. A group of mathematical barnacles then show that, if several barnacles look at the same imaginary object and record the angle it subtends from their own position, it is possible to predict when it will become real, and for whom. The barnacles abandon their idealistic philosophy, and become good materialists. Then an ingenious barnacle points out that, if one substitutes certain values into the equations, one is led to predict the existence of an object beneath the surface of the rock. And everyone knows that there is nothing beneath the rock. Relieved, the barnacles return to their idealism and religious belief.

Haldane's mixture of science, imagination and agnosticism opened my mind to a new way of thinking. It was a liberation that has lasted my lifetime. Haldane and

Stapledon also introduced me to the importance of evolution. But neither was a naturalist. The link between evolution and natural history I learnt from Darwin, who was a supreme naturalist. For him, new general ideas originated in particular observations of natural history.

I must return to 1947, when I decided to leave engineering and become a biologist. I enrolled as a student of zoology at University College London because I knew that Haldane was a teacher there. I was already 27, which seems old to start an undergraduate degree, but in 1947 it was easy, because many of my fellow students were of much the same age, returning to study after time in the services. It was at UCL that at last I learnt, primarily from Haldane, how to put mathematics and biology together. While still an undergraduate I wrote several papers on animal locomotion－particularly flight. I had considerable difficulty getting these published: one paper on the origin of bird flight was rejected on the grounds that the author knew no aerodynamics, which rather annoyed me. After graduating, I stayed at UCL as Haldane's graduate student, and later as a lecturer in the zoology department. I worked alongside Haldane and his wife Helen Spurway until they left for India, I think in 1960. Most of my research prior to 1960 was experimental, on the fruitfly Drosophila subobscura. I do not reget this experimental apprenticeship: it has been valuable to know the genetics, physiology and behaviour of one species really well.

One detail from my early days at UCL is worth recording. Motoo Kimura visited Haldane, I think in 1952, and stayed in our house during his visit. At that time I had never heard of game theory, and so far as I know Motoo had not started thinking about molecular evolution. When, later, he did publish his idea that many gene changes in evolution occur, not because the new gene is positively selected, but because it is 'neutral', the theory was unpopular with most British evolutionary biologists. They saw him as anti-Darwinian, which I think is a mistake. Perhaps because we had met, and liked one another, I was more sympathetic to his ideas. Today. I think most of us see him as one of the most original and creative biologists of his generation.

I left UCL in 1965 to become the first professor of biology at the new University of Sussex. This was fun. I could do more or less what I liked, and start a school of biology as I thought it ought to be. Although I made some mistakes, I am pleased with the results. I still work in the school as a retired professor, with no duties but plenty of young people to talk to.

Three main questions have interested me during my career as a biologist: the evolution of ageing, of ritualized behaviour, and of sex. In retrospect, I can see what these three topics have in common that stimulated my interest: at first sight, none of the three makes sense in terms of natural selection. Why should an animal deteriorate with age? Surely it would leave more descendants if it did not. Why are ritualized signals believed? I return to this question in a moment. Most puzzling of all, why reproduce sexually? A female who dispensed with a mate, and produced only daughters by virgin birth, would leave twice as many descendants like herself as would a sexual female. Perhaps my main contribution to the ‘evolution of sex’ debate has been to ask the right questions. I think it is fair to say that the field is still the most puzzling and controversial in evolutionary biology.

For me, the question about ritualized behaviour has proved to be the most fruitful. As a student in 1947, I learnt that Konrad Lorenz had emphasized that animal conflicts are often ‘ritualized’: instead of fighting all out, they display their aggressive intent by signals, like a man shaking his fist at an opponent. Quite often, disputes are settled by such signals, without escalation. The standard explanation at the time was that such behaviour had evolved because escalated fighting leads to injuries that are bad for the survival of the species. Even as a student I knew that this has to be nonsense. Natural selection does not lead to the evolution of traits that favour the survival of whole species, but of individuals. But although I knew that there was a puzzle here, I did not think about it seriously for twenty years.

In 1970, after five years running the school of biology at Sussex, I took a term off in Chicago, I decided I would spend my time thinking about animal contests, and as a preparation would learn about the Theory of Games, a branch of mathematics that models human conflict situations. I started by taking out of the library The Theory of Games and Economic Behaviour by Von Neumann and Morgenstern, the founding fathers. I found it incomprehensible－the book seemed to spend many pages proving the obvious. Fortunately, instead of abandoning my plan, I read a simpler text on the subject. At first sight, it also seemed of little use. Essentially, it asks the following question. I am in a dispute with you. If I am rational, and assume that you are also rational, what should I do? But animals are not rational (people aren’t either, but that is another matter), so what good is the theory of games to a biologist? At the time, the main thing that I could borrow was a mathematical notation for describing contests, which I found extremely useful. A good notation is often half the battle.

What I needed to do was to combine game theory with the idea of natural selection. What strategy would evolve from the application, not of reason, but of selection? The answer is that the strategy that will evolve is what I called an ESS－short for ‘evolutionarily stable strategy’. I can best explain the idea by an example－not the one I had in mind when I invented the idea of an ESS, but a simpler one. Why, in almost all sexual species, are there equal numbers of males and females? Imagine that a female can choose the sex of each child she produces: I will call this her ‘strategy’. (We would get the same answer if we assumed that it was the father that chose the sex of the child. Also, it is nearer the truth if we suppose that she chooses, not the sex of each child, but the probability that each child will be a boy or girl.) Which sex should she choose? Her choice will be determined by natural selection, so as to maximise the number of her grandchildren. Clearly, she should produce a child of whichever sex is rarer in the population, because members of the rarer sex produce, on average, more children. So, if there are more boys being born than girls, she should produce a daughter, and if more girls than boys she should produce a son. If the ‘strategy’ is inherited, then the stable state of the population is one with equal numbers of boys and girls－that is, one in which a female produces sons and daughters with equal probabilities.

For the sex ratio game, then, the ESS is to produce equal numbers of boys and girls. This is an ‘unbeatable’ strategy, in the sense that, if everyone else is doing it, there is no alternative strategy that would do better. The idea is very general. Whenever there is a conflict of interest between members of a population, it is usually the case that the best thing to do depends on what others are doing. And whenever this is the case, evolution will lead to an ESS. (If one exists. There are games which have no ESS－an example is the children’s game of ‘Rock-Scissors-Paper’).

While in Chicago, I derived the formal conditions for a strategy to be an ESS. This is mathematically rather easy. I set it as a problem to a class of graduate students I was teaching, and most of them solved it without difficulty. To be honest, when I first thought of the idea I thought it was rather trivial－mathematically it is trivial. But it turns out to be a simple idea that can be applied to an astonishingly wide range of problems. The first applications were to conflict behaviour in animals, but it has since been applied not only to a range of behaviour patterns in animals, but to plant growth, and even to the evolution of viruses.

I will describe briefly how I came to realise how flexible the method can be. I started by inventing a model of animal conflicts that I called the Hawk-Dove game. Animals compete for a resource of relatively small value. They can either fight all out (Hawk), or display and run away if their opponent attacks (Dove). If everyone else is a Dove, it pays to be a Hawk－you get the resource for nothing. But if Hawks are common, it pays to be a Dove, because the resource is not valuable enough to be worth fighting for. The ESS turns out to be ‘Sometimes play Hawk, sometimes play Dove’－the frequency depending on the value of the resource and the cost of fighting. But it then occurred to me that, if two humans were faced with such a game, they would surely toss for it. Obviously, animals cannot toss coins, but is there anything else they can do?

All that tossing a coin does is to introduce an asymmetry into an otherwise symmetrical situation. Perhaps, I thought, animals can use some other kind of asymmetry to settle contests. The obvious one is what I called ‘ownership’－one animal has been in possession of a resource, for example a territory, for some time and the other is an intruder. If so, the strategy ‘If you have been in undisputed possession of the resource for some time, play Hawk: if not, play Dove’ might be an ESS. For obvious reasons, I called this strategy ‘Bourgeois’. It is easy to show that, if the possible strategies are Hawk, Dove and Bourgeois, then Bourgeois is the only ESS.

At this point I got worried. Surely animals cannot evolve a respect for ownership. I suspected that my Hawk-Dove-Bourgeois game was a fantasy with no connection with the real world. However, I was invited to give a seminar in Austin, Texas, and decided I would talk about my new idea of an ESS. At the end, I described the Bourgeois strategy, but added that I did not think that real animals would be able to adopt it. When I sat down, a young man in the audience－I now know him as Larry Gilbert－got up and said he would like to describe the work he had done for his doctorate in California on a Swallowtail Butterfly. In the breeding season, the males occupy territories on hilltops. A female ready to mate flies uphill, where she finds a male and mates with him. The only snag is that there are more male butterflies than hilltops. If a male seeking a territory flies uphill, he will usually find the hilltop already occupied. There follows a brief spiral flight, during which the two males circle one another, before one of them retreats. Larry found that it is always the intruder that retreats and the owner that remains in possession. He then persuaded two males that they owned the same hilltop, by allowing one of them to occupy the hilltop on Monday, Wednesday and Friday, and the other on Tuesday, Thursday and Saturday. Then, on a Sunday, he released both males simultaneously. There ensued a prolonged spiral flight, quite unlike any that occurs normally: both of them were behaving like Hawks.

I think it was at that moment that I first thought that the idea of an ESS might prove to be fruitful. A lot has happened since then. The idea has been made more rigorous, and shown to be compatible with Mendelian genetics. It has been widely applied－it has even been possible to find an animal－a lizard－that plays the Rock-Scissors-Paper game: as predicted, the frequencies of the three possible strategies in the population cycle continuously. My own interest at present is in the evolution of animal signals, and in particular in understanding why such signals are reliable. It turns out that game theory is the standard way of studying this problem.

Perhaps it is possible to draw some lessons from the story of evolutionary game theory. First, although the mathematics is trivial, it is still important to have a formal model, because only when such a model exists is it possible to see exactly what is being assumed. Verbal models can always be interpreted in different ways－as a European I think of the doctrine of the Trinity, but I feel sure that similar examples exist in the history of Japan. Second, a good model must be simple. Evolutionary game theory assumes that offspring resemble their parents, but ignores all genetic details. It was important, later, to investigate how far the conclusions stand up when genetic detail is incorporated, but the model would have been hopelessly cumbersome if genetics had been included from the outset. Finally, one knows one has succeeded when some animal turns out to be doing something odd that is predicted by the theory: that is happiness.