What is Life?: Schrodinger's Influence on Biology

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COMMENTARY

WHAT IS LIFE?: SCHRÖDINGER'S INFLUENCE ON BIOLOGY[1]

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Schrödinger's contribution to biology centers around his book *What is Life?*, first published in 1944, which stemmed from a series of public lectures he gave at Trinity College, Dublin, in 1943. The book was widely read at the time, and continued to be read widely right through the 1950s. In fact, the book is still in demand today. It was reviewed everywhere that mattered, was translated into a number of languages, and has become a classic in popular science.

There is no doubt that the book was widely discussed. There is also no doubt that it has become part of the folklore of biology. The book played a key role both in recruiting "exact" scientists into the field and in directing the course taken by molecular biology in the formative years of the 1950s. In this respect it has been the subject of a number of studies by historians of science.

Here I want to delve a little into the reasons for this passage of the book into folklore, and to give a personal and preliminary assessment of the influence that Schrödinger, via the book, has had in biology. First I will sketch something of what was known about biology, and more specifically genetics and biochemistry, in the early 1940s, and then briefly go through the book itself, to indicate just what Schrödinger wanted to put across. Finally, after this background, I want to discuss the possible influences the book has had on biologists and biology.

GENETICS AND BIOCHEMISTRY IN 1940

Mostly through research with maize and with the fruit fly *Drosophila*, the foundations of genetics were firmly established by 1940. It was known that heredity was determined by genes located on chromosomes, and that each of the cells comprising any organism contains a chromosome set. When cells divide, genes are duplicated in mitosis. The only exception is during sexual processes, which are accompanied by meoisis. Occasionally a new variant of an organism, a mutant, arises spontaneously, and this variation is associated with a change in a specific gene. A particularly exciting result dating from 1927 was that mutations could be induced by irradiating organisms, in this case *Drosophila*, with X-rays. The genetic determinants derived from the two parents in a mating were known to be mixed in the offspring by a process of recombination, and this knowledge had been already utilized to map the determinants for various characters at specific locations on a chromosome.

It had been known for a long time that the important molecules associated with living organisms contain carbon — thus the term "organic" chemistry. Much was known about

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[1] Based on a talk given at the Dublin Institute for Advanced Studies in October, 1983.

[Editor's Note: *What is Life? The Physical Aspect of the Living Cell*, by Erwin Schrödinger, was originally published in 1944 by Cambridge University Press. In subsequent printings Schrödinger added notes to some chapters. The book is currently available in a reprint edition, bound with *Mind and Matter*, published by Cambridge University Press.]

small organic molecules such as alcohols and esters; the atoms forming these molecules were held together by covalent bonds, the nature of which had been first explained in terms of quantum theory by London and Heitler in 1926. Much larger "macromolecules" with molecular weights of between 10^4 and 10^5 were also known to exist in cells, including enzymes that accelerate reactions. There was some early knowlege about the composition of other proteins, and an awareness that nucleic acids were also present in cells. But techniques were not available to investigate these macromolecules in detail. There was no X-ray crystallography, chromatography or electron microscopy. The only meager evidence of the size and shape of these macromolecules came from studies using centrifugation.

This, very briefly, was the state of knowledge when Schrödinger's book appeared. The foundations of formal genetics were well laid, but there were no real ideas about biochemical genetics (that is, about the chemical composition of genes or how they act), although there was a suspicion that genes were proteins and that they controlled the synthesis of other proteins.

SUMMARY OF *WHAT IS LIFE?*

At the very start of his book Schrödinger sets its main question in these words:

> How can the events *in space and time* which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?

And the answer to this question he also gives at the beginning of the book, in these terms:

> The obvious inability of present-day physics and chemistry to account for such events is no reason at all for doubting that they can be accounted for by these sciences.

The book itself consists of seven chapters. The first three are by way of introduction to the main argument. Early on in the first chapter he makes the point that organisms exhibit extremely orderly behavior, and that this in turn must reflect the operation of precise physical laws. He goes on to say that, in classical physics, physical laws rest on atomic statistics, that they are only approximate, and that their precision is based on the intervention of large numbers of particles. He gives a number of examples, including paramagnetism, Brownian movement, and diffusion. Finally, he discusses the degree of accuracy that can be expected from such a physical law in terms of the square-root of the number of particles taking part in a reaction, and shows that this argument leads directly to the conclusion that for orderly behavior the number of particles contained in the key parts of an organism must be extremely large.

The next two chapters give a clear resumé of what was known about formal genetics in the 1940s. They start by emphasizing that heredity is determined by a code-script enshrined in the chromosomes. There is then a summary of the properties of genes and of the processes of mitosis, meoisis, and crossing-over. This is followed by a section that considers the genetic and cytological evidence bearing on the size of genes, which put an upper limit on them of about 10^6 atoms. Finally comes a discussion of the nature of mutations, with particular attention being given to the experiments on the induction of mutants with X-rays.

The real argument of the book begins in Chapter 4, and starts by posing an apparent paradox. The mere fact that we speak of hereditary properties indicates that we recognize they have an almost absolute permanence. This permanence must be determined by the structure of the genetic material. Also determined by the structure of the genetic material must be the ability of a gene to mutate into another stable state. And all this has to be accomplished by a gene containing less than 10^6 atoms. This requirement is inexplicable in terms of classical physics. The answer to the paradox must be therefore that genes are stabilized by some non-classical force. The obvious candidate is the covalent bond, that peculiarly quantum phenomenon which gives stability to molecules. In other words, a gene must be a macromolecule. Schrödinger acknowledges that in one sense to say that a gene is a macromolecule is a trivial statement, in that even if it had not been stated precisely before, the idea was clearly implicit in a number of genetic discussions. His whole point was to emphasize, however, that in order to understand life — the stability and permanence of the genetic material—classical physics was inadequate, and one had to go to the very basis of quantum theory.

In the next chapter he develops the thesis that a gene is a macromolecule held together by quantum forces. He takes up an idea that was proposed around 1935 by Max Delbrück, himself a quantum physicist, that a gene can be likened to a stable state of a quantum mechanical system. A mutation can then be considered as a discontinuous shift of this stable state to another, the change occurring spontaneously or being induced by X-rays or some other disturbance. He discusses this scheme of Delbrück in some detail, and concludes that it can explain in a natural way all the facts that were known at the time about the stability of genes and about the frequencies of spontaneous and induced mutations.

Among these considerations, almost as an aside, he introduces two small sections that encapsulate ideas that are probably the most original in the whole book, and have become absorbed into the fabric of modern biology. The first of these makes an analogy between a gene and an aperiodic crystal and is best explained in Schrödinger's own words:

> A small molecule might be called "the germ of a solid." Starting from such a small solid germ, there seem to be two different ways of building up larger and larger associations. One is the comparatively dull way of repeating the same structure in three directions again and again. That is the way followed in a growing crystal. Once the periodicity is established, there is no definite limit to the size of the aggregate. The other way is that of building up a more and more extended aggregate without the dull device of repetition. That is the case of the more and more complicated organic molecule in which every atom, and every group of atoms, plays an individual role, not entirely equivalent to that of many others (as is the case in a periodic structure). We might quite properly call that an aperiodic crystal or solid and express our hypothesis by saying: We believe a gene—or perhaps the whole chromosome fibre—to be an aperiodic solid (p. 60).

The second of the ideas, which had not been expressed explicity before, was a clear statement indicating the necessity for a genetic code:

> It has often been asked how this tiny speck of material, the nucleus of the fertilized egg, could contain an elaborate code-script involving all the future development of the organism? A well-ordered association of atoms, endowed with sufficient resistivity to keep its order permanently, appears to be the only conceivable material structure, that offers a variety of possible ("isomeric") arrangements, sufficiently large to embody a complicated system of "determinations" within a small spatial boundary. Indeed, the number of atoms in such a structure need not be very large to produce an almost unlimited number of possible arrangements (p. 61).

And he goes on to illustrate the last point with the example of the Morse code.

In the last two chapters Schrödinger takes up another line of argument. No specific information about how genes work can be expected to come from the very general proposal of Delbrück concerning genes and quantum states; that is a subsequent problem for biochemistry and genetics. But, he goes on:

> . . . there is just one general conclusion to be obtained from it, and that, I confess, was my only motive for writing this book.
>
> From Delbrück's general picture of the hereditary substance it emerges that living matter, while not eluding the "laws of physics" as established up to date, is likely to involve "other laws of physics" hitherto unknown, which, however, once they have been revealed, will form just as integral a part of this science as the former" (p. 68).

The argument that leads to this conclusion runs thus. Consider how a single cell, the germ cell, turns into an organism. It does this via a series of reactions, each one of which has to be exquisitely tuned in order that the complex organism should have the characteristics determined by the code-script contained in the genes. It seems that orderliness is increased in the system. How can one explain this? There are in fact two problems. One concerns entropy, because superficially the entropy of the system seems to decrease, which is contrary to the second law of thermodynamics. This problem of entropy in living organisms is not too difficult to dispose of, as one can enlarge the system to include the environment, and then consider how the developing organism can feed on energy, or "negative entropy," as

Schrödinger calls it. This is a classical argument and does not introduce any new ideas.

The more subtle problem is that living organisms seem to be examples where order of one kind, that which originally is in the codescript of the genes, breeds order of a different kind, that of the concerted reactions that occur during the development of an organism. This situation, where a small number of molecules determine a whole series of ordered reactions with fantastic accuracy, is unknown in ordinary physical and chemical systems, and suggests that underlying it there may be new laws of an "order breeding order" kind.

INFLUENCE OF *WHAT IS LIFE?* ON BIOLOGY

In discussing the influence of Schrödinger's book on biology it is useful to distinguish between two questions. The first is its effect on bringing scientists, particularly physicists, into biology. The second is its effect in introducing new ideas into biological research.

At this point I want to emphasize, in responding to these questions, that I am putting forward my preliminary reflections. This is partly because any assessment made of the role of the book involves talking to scientists who were working in biology at the time, the 1940s and 1950s, and I have talked with only a limited number of them. It is also partly due to the realization that it is virtually impossible to believe most of what one is told about things that happened 30 to 40 years ago. If you ask a scientist what the influence of the book was on his or her scientific career, you may be told quite a detailed story. If you come back a few days later and ask the same question again, the chances are that you will be told something completely different. Having said that, however, as Schrödinger says in his preface, "some of us have to be willing to express opinions based on incomplete knowledge—at the risk of making fools of ourselves." So let us consider the question of whether there were many exact scientists who took up biology because of the book?

One who did was Maurice Wilkins, one of the important figures in elucidating the structure of the genetic material, DNA. During World War II he was working at the Atomic Energy Project, in Chalk River, Ontario, on atomic research, when Harold Massey gave him the book to read. Soon after that he decided to opt for biophysics, rather than continue his career in atomic science. No doubt there are others I do not know of who also changed to biology at that time. But one must remember that a contributing factor for some physicists was, as with Wilkins, the desire to get away from atomic research and its connections with their war experience.

And there was another contributing factor that I may as well illustrate by talking about myself. Schrödinger certainly turned me into a biologist. I worked with him on unified field theories between 1948 and 1950 in Dublin. Early in 1950 he asked me whether I had considered what I was going to do when my scholarship ran out, and went on, "Einstein and I have been trying to get somewhere on unified field theories for the past 10 years, and it's unlikely you will get anywhere on your own. So it is time to think of doing something else. Either you learn some quantum theory or you do something quite different. I would suggest you try biology." So I said yes. This yes however, was colored by the fact that at that time quantum theory was passing through a difficult phase. It was the period just before relativistic quantum mechanics and every calculation, I seem to remember, gave infinity as an answer. The skill was to lay down rules that would let you subtract infinity from infinity and get something meaningful. It was as far away from unified field theories as biology.

Obviously one needs much more talking to other contempories, and being skeptical of what they say, to determine just how many physicists and chemists *did* become biologists because of the book. But if we limit the question to those changing to biology between 1944 when the book first appeared, and 1953 when the structure of DNA was proposed, I would say the number was very small. This is because few scientists of any kind moved into biochemical genetics at that time. It was still a period of laying the groundwork by relatively simple biological (or biophysical) techniques far removed from quantum theory or the code. And the people who came in from other fields and did get involved did so, not mainly because of Schrödinger's book, but because of personal contacts they had. For example, Watson entered the field due to the influence of Luria, Benzer and Stent were influenced particularly by Delbrück, and in my case it was not reading Schrödinger's book which induced me to come a biologist, but the personal influence of Schrödinger himself.

The second and more difficult question is whether the book influenced the direction of biological research. Again one can quote cases where Schrödinger's ideas were taken up directly. The notion that most appealed to theoretical physicists, I think, was that you could consider a gene as a quantum mechanical system: and the explanation of mutations induced by X-rays was interpreted as being due to a change from one stable state to another. Cryus Levinthal was so taken by this idea that in the early 1950s he spent a year building a UV-monochromator to measure the UV-absorbance of "wild-type" and mutant genes. Before he completed the apparatus he gave up the project, because it had become apparent by that time that the simple idea that ionizing radiation could induce a mutation by causing a gene to jump from one stable state to another was not correct. The explanation was much more subtle, and was one that could not conceivably have been arrived at by Schrödinger in 1943.

Another approach that was attempted was the direct application of quantum theory to problems involving the interaction of genes. One particular system on which a number of calculations were made concerned the specific interaction which brings indentical genes together in the initial pairing step of meiosis that lead to genetic recombination. None of these calculations was ever successful, however, because in retrospect they never took into account the role of the hydrogen bond, or of specific enzymes, in mediating molecular interactions.

The other ideas of Schrödinger that showed tremendous insight at the time, that the gene could be likened to an aperiodic crystal with its information contained in a code-script, also had little influence during the decade after the book appeared. This was because they were really ahead of their time. Experimentally, as has just been indicated, this was the period when genetic systems were being developed (using bacteria and bacterial viruses) that could be utilized to answer biochemical and genetic questions. These studies led to the identification of DNA as the genetic material, and were followed by the elucidation of its structure in 1953. In the light of this structure the ideas about the aperiodic crystal and the code became almost obvious, and were soon generally accepted.

The final problem raised in the book, and to Schrödinger the most important one, was the question as to whether a basic understanding of biological systems would lead to the introduction of new physical laws. This was the goal that brought a number of important physicists to think about biology in the 1940s and 1950s. Bohr had regularly organized symposia and workshops in Copenhagen, and Delbrück had received his initial stimulus from these sessions. Both hoped that the solution as to how biological systems replicated and developed would lead to some new "principles of uncertainty" which would add a new dimension to ideas about physics. This was not to be, however. Schrödinger's approach was quite different. He was fascinated by the principle of orderliness which underlined the whole growth and development of living organisms; that is, the scheme which ensures the orderly transfer of information from the code-script in the gene to the myriad reactions which have to be perfectly coordinated in order that the finished organism, with its unique characteristics, should be successfully produced. Although the complete answer as to how this occurs is still not known, it is now realized that no fundamental new principles are involved. The answer depends partly on the existence of very subtle feedback mechanisms involved in gene regulation, and also on the unique properties of a number of biological molecules which play key roles during biological growth. There is no doubt, however, that Schrödinger appreciated the crucial importance of this most difficult biological problem with uncanny foresight. But his hopes for a new type of physical law were not borne out.

So, in summary, my feeling is that *What is Life?* had little direct influence either in recruiting physicists or chemists into biology, or in affecting the direction taken by research in molecular biology. Did the book have any real influence then? Is there any truth to the myth of its importance? I think the answer is yes. But that influence was after 1953, rather than before, and more indirect than direct. The elucidation of the structure of DNA heralded a turning point in the development of molecular biology. After that time a lot of gifted young scientists entered the field. Molecular biology vied for the first time with theoretical physics as a venue for the brighter students. This was a completely new situation, and depended obviously on the consequences that could already be sensed would emanate from knowing the DNA structure. But it was also sparked to quite an extent by the stimulation that came from reading Schrödinger's book (still being widely read as before) that allowed one to talk about molecular biology in terms of quantum theory and crystals and the code. Biology stopped being a "sissy" subject and came of age.

As a postscript to these reflections it is perhaps pertinent to add one more that intrigues me. What aroused Schrödinger's interest in Biology? Let me quote from a memo concerning Warren Weaver. Weaver himself was a not very successful theoretical physicist who became an incredibly successful head of the Biology Division of the Rockefeller Foundation. He funded virtually every molecular biologist who showed promise in the years before and immediately after the war, and he knew Schrödinger from the 1930s. The memo refers to a visit to Dublin made in 1950.

> . . . Warren Weaver had rather hoped to discover that Schrödinger has both a serious and an active interest in applying various concepts of theoretical physics to biological problems; but it turns out that Schrödinger's book "What is Life?" was written as a purely personal venture and — to use Schrödinger's own words — "as a hobby." Furthermore, there is no one else in his place who has any interest whatsoever along this line. This, incidentally, is true even of the Australian, N. Symonds, who had raised the question of a possible fellowship to work for a year with Rashevsky. Symonds knows no biology and has done absolutely nothing in biophysics, but merely thought that it might be interesting to try!

This memo firmly puts me in my place, but much more importantly illustrates an intriguing facet of Schrödinger. Although his major scientific interests were quantum theory and relativity theory, he also loved to grapple with many different kinds of problems. He wrote books about philosophy, about the mind, about thermodynamics, and in quite a different vein he also wrote poetry. Somewhere along the line the problems tackled in *What is Life?* confronted him, were thought about, the lectures were given and the book written, and then the episode was forgotten as he moved on to think about something else. I have never met any other scientist quite of this mold.