

Physics and the riddle of life

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Erwin Schrödinger's book What is Life?, published in 1944, drew several of the brightest physicists into molecular biology. But the book's chief merit lies in its rescue from obscurity and popularization of an earlier paper by Timoféeff, Zimmer and Delbrück.

IN THE early 1940s, Schrödinger worked at the Institute for Advanced Studies in Dublin. One day he met P.P. Ewald, another German theoretician who was then Professor at the University of Belfast. Ewald, who had been a student in Göttingen before the First World War, gave Schrödinger a paper that had been published in an obscure journal in 1935¹. It was by N.W. Timoféeff-Ressovsky, K.G. Zimmer and Max Delbrück and was entitled "The Nature of Genetic Mutations and the Structure of the Gene"². Apparently Schrödinger had been interested in that subject for some time, but the paper fascinated him so much that he made it the basis of a series of lectures at Trinity College, Dublin, in February 1943; they were published by Cambridge University Press in the following year under the title *What is Life? The Physical Aspect of the Living Cell*.

The book is written in an engaging, lively, almost poetic style ("The probable life time of a radioactive atom is less predictable than that of a healthy sparrow"). It aroused wide interest, especially among young physicists. Up to 1948 it drew 65 reviews and has probably by now sold 100,000 copies. It is still in print and has become a classic, providing nourishment for historians, sociologists and philosophers of science who have commented on it, on the comments on it or on the comments on the comments on it. A PhD thesis published on the subject in 1979 contains over 120 references, excluding the 65 reviews¹. François Jacob has explained the reasons for the book's impact best:

After the war, many young physicists were disgusted by the military use that had been made of atomic energy. Moreover, some of them had wearied of the turn experimental physics had taken . . . of the complexity imposed by the use of big machines. They saw in it the end of a science and looked around for other activities. Some looked to biology with a mixture of diffidence and hope. Diffidence because they had about living beings only the vague notions of the zoology and botany they remembered from school. Hope, because the most famous of their elders had painted biology as full of promise. Niels Bohr saw it as the source of new laws of physics. So did Schrödinger, who foretold revival and exaltation to those entering biology, especially the domain of genetics. To hear one of the fathers of quantum mechanics ask himself: "What is Life?" and to describe heredity in terms of molecular structure, of interatomic

bonds, of thermodynamic stability, sufficed to draw towards biology the enthusiasm of young physicists and to confer on them a certain legitimacy. Their ambitions and their interests were confined to a single problem: the physical nature of the genetic information³.

Seymour Benzer, Maurice Wilkins and Gunther Stent have said that the book was decisive in drawing them from physics into biology. Francis Crick told me that he found it interesting, but that he would have switched to biology anyway. I was



Erwin Schrödinger: engaging writer.

already in the thick of trying to solve the structure of proteins when it was published, and I may have been encouraged by its quotation of Darlington's view that genes are made of protein. Crick wrote in 1965:

On those who came into the subject just after the 1939-1945 war Schrödinger's little book . . . seems to have been peculiarly influential. Its main point — that biology needs the stability of chemical bonds and that only quantum mechanics can explain this — was one that only a physicist would feel it necessary to make, but the book was extremely well written and conveyed in an exciting way the idea that, in biology, molecular explanations would not only be extremely important but also that they were just around the corner. This had been said before, but Schrödinger's book was very timely and attracted people who might otherwise not have entered biology at all⁴.

However, in 1970 Crick added:

I cannot recall any occasion when Jim Watson and I discussed the limitations of Schrödinger's book. I think the main reason for this is that we were strongly influenced by Pauling, who had essentially the correct set of ideas. We therefore never wasted any time discussing whether we should think in the way Schrödinger did or the way Pauling did. It seemed quite obvious to us we should follow Pauling⁵.

Nor can I recall Crick, Watson, Kendrew and myself ever discussing the bearing of Schrödinger's book on structural molecular biology during our years together at the Cavendish Laboratory; Stanley Cohen writes that few of the many scientists participating in Delbrück's phage course at Cold Spring Harbor in 1944 had read Schrödinger "and in all the social and intellectual activities of these [post-war] summers I do not recall any mention of Schrödinger". The participants included such pioneers of molecular genetics and biochemistry as Luria, Hershey, Lwoff, Monod and Brachet. Hence the book does not appear to have had much impact on the people already working in the field.

Schrödinger's book is written for the layman and begins with a chapter entitled "The Classical Physicist's Approach to the Subject". He asks how events in space and time taking place in a living organism can be accounted for by physics and chemistry.

Enough is known about the material structure of life to tell exactly why present-day physics cannot account for life. That difference lies in the statistical point of view. It is well-nigh unthinkable that the laws and regulations thus discovered [i.e. by physics] should apply immediately to the behaviour of systems which do not exhibit the structure on which these laws and regularities are based.

Schrödinger jumps to that conclusion after reading that genes are specific molecules of which each cell generally contains no more than two copies. He had entered Vienna University in 1906, the year that Boltzmann died, and had been taught physics by Boltzmann's pupils. He remained deeply influenced by Boltzmann's thoughts throughout his life. According to Boltzmann's statistical thermodynamics, the behaviour of single molecules is unpredictable; only the behaviour of large numbers is predictable. In genetics, therefore, Schrödinger concludes, "we are faced with a mechanism entirely different from the probabilistic



N.W. Timoféeff-Ressovsky and (right) K.G. Zimmer: the co-authors with Delbrück of the 'Green Pamphlet', the paper which, in paraphrased form, constitutes the backbone of Schrödinger's book.

ones of physics". This difference forms the guiding theme of his book.

In the first chapter, Schrödinger illustrates the meaning of statistical thermodynamics by the examples of Curie's Law, of Brownian motion and diffusion, and of the \sqrt{n} rule. His next two chapters, on hereditary mechanisms and on mutations, give brief popular introductions to textbook knowledge on these subjects available at the time. They reveal one vital misconception in Schrödinger's mind: "Chromosomes", he writes, "are both the law code and the executive power of the living cell". In fact, biochemists had shown that the executive power resides in enzyme catalysts, and in 1941 G.W. Beadle and E.L. Tatum discovered that single genes determine single enzymatic activities⁶; that discovery led to the one-gene-one-enzyme hypothesis, a most fruitful idea that had already been foreshadowed by the Cambridge biochemist and geneticist J.B.S. Haldane⁷. Schrödinger does not appear to have heard of this.

The next two chapters form the backbone of his book; they are called "The Quantum-Mechanical Evidence" and "Delbrück's Model Discussed and Tested", and are largely paraphrased versions of the paper by Timoféeff, Zimmer and Delbrück⁸. That paper covers 55 pages and is divided into four sections. The first section, by Timoféeff, describes the mutagenic effects of X-rays and γ -rays on the fruitfly *Drosophila melanogaster*. He shows that the spontaneous mutation rate of the fly is low, and that it is raised about five fold by a rise in temperature of 10°C. Ionizing radiations increase that rate as a linear function of the dose, independent of its time distribution, of the wavelength and of the temperature during irradiation.

The second section of the paper is by Zimmer and applies the target theory to Timoféeff's results. The number of mutations $x = a(1 - e^{-kD})$ where a and k are constants and D is the dose. Zimmer next asks whether the mutations had arisen by the direct absorption of quanta, by the passage of secondary electrons through a sen-

sitive volume or by the generation of ion pairs. If the dose is measured in roentgens, the number of quanta required to produce a given dose diminishes with diminishing wavelength. Thus direct absorption of quanta is inconsistent with the linear dependence of the mutation rate on the dose. The same applies to secondary electrons. Only the number of ion pairs is proportional to the dose, obviously, because that is how the dose is measured.

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Zimmer therefore concludes that a single hit suffices for the production of one mutation and that this hit results either in the formation of an ion pair or a transition to higher energy.

The third section of the paper is by Max Delbrück and bears the title "Atomphysikalisches Modell der Mutation" ("A Model of Genetic Mutation Based on Atomic Physics"). Delbrück reminds us that the concept of the gene began as an abstract one, independent of physics and chemistry, until it was linked to chromosomes and later to parts of chromosomes which were estimated to be of molecular size. Since he and his colleagues had no means of discovering the chemical nature of genes directly, they attacked the problem indirectly by studying the nature and the limits of their stability and by asking if these were consistent with the knowledge that atomic theory has provided about the behaviour of well-defined assemblies of atoms.

Such assemblies can undergo discrete and spontaneous transitions of vibrational and electronic states. Vibrational transitions are very frequent and involve no chemical changes. From electronic transitions the assemblies may either revert to the ground state or reach a new equilibrium state after undergoing an atomic rearrangement, for example to a tautomeric form. The five-fold rise in spontaneous mutation frequency for a 10°C rise in

temperature leads Delbrück to derive an activation energy of $\sim 1.5\text{eV}$ and an average lifetime of a few years when half the molecules composing the gene will have undergone an electronic transition.

Delbrück then describes how, on average, X-rays lose energy to secondary electrons in portions of 30eV per ionization, which is $1,000 \times kT$ and 20 times the energy of activation of 1.5eV needed for a spontaneous mutation. However, to produce as much as 1.5eV, the ionization must not occur too far away from its target. We knew too little about the ways in which the energy of photoelectrons is dissipated to determine the absolute value of the dose needed to induce a mutation with a probability of unity, but that dose, expressed as the number of ionizations per unit volume, was likely to be about 10 – 100 times smaller than the number of atoms of the gene per unit volume. Delbrück now calculates that dose as follows.

A frequently observed X-ray mutation (eosin) occurs with a dose of 6,000r once in 7,000 gametes. Hence a probability of unity of its occurrence needs a dose of $42 \times 10^6\text{r}$. 1r produces $\sim 2 \times 10^{12}$ ion pairs in 1ml H_2O , whence $42 \times 10^6\text{r}$ produce $\sim 10^{20}$ ion pairs. Since 1ml H_2O contains $\sim 10^{23}$ atoms, this means that at least one in a thousand atoms becomes ionized. However, Delbrück cautiously refrains from concluding that a gene is likely to consist of a thousand atoms.

Schrödinger used Delbrück's result to point out "that there is a fair chance of producing a mutation when an ionization occurs not more than about 10 atoms away from a particular spot on the chromosome", but research published while Schrödinger was writing his book showed such calculations to be meaningless. In a paper that appeared in June 1944, Joseph Weiss pointed out that the biological effects of ionizing radiation are due principally to the generation of hydroxyl radicals and hydrogen atoms in the surrounding water⁹. Collinson, Dainton, Smith and Tazuke¹⁰, and independently Czapski and Schwartz¹¹, later discovered that the supposed hydrogen atoms were in fact

hydrated electrons¹². Hydroxyl ions and hydrated electrons have half lives of ~1 ms (assuming a concentration of 1 μ M H₂O₂) and 0.5 ms respectively, in which times they can diffuse to their targets even if they are generated more than a thousand atomic diameters away from them.

Delbrück concludes that it is premature to make the description of the gene any more concrete than the following:

We leave open the question whether the single gene is a polymeric entity that arises by the repetition of identical atomic structures or whether such periodicity is absent; and whether individual genes are separate atomic assemblies or largely autonomous parts of a large structure. i.e. whether a chromosome contains a row of separate genes like a string of pearls, or a physico-chemical continuum.

I found the Timoféeff-Zimmer-Delbrück paper and especially Delbrück's part, most impressive. Delbrück was a theoretical physicist whose interest in biology had been aroused by Niels Bohr's lecture "Light and Life", delivered in Copenhagen in 1932. In that lecture, Bohr had said:

The existence of life must be considered as an elementary fact that cannot be explained, but must be taken as a starting point in biology, in a similar way as the quantum of action, which appears as an irrational element from the point of view of classical mechanical physics, taken together with the existence of elementary particles, forms the foundation of atomic physics. The asserted impossibility of a physical or chemical explanation of the function peculiar to life would be . . . analogous to the insufficiency of the mechanical analysis for the understanding of the stability of atoms¹³.

The search for Bohr's elementary fact of life had fired Delbrück's imagination. He was only 29 years old, working as assistant to Otto Hahn and Lise Meitner in the Kaiser Wilhelm Institut für Chemie in Berlin and doing his biological work as a side line, but his paper shows the maturity, judgement and breadth of knowledge of someone who had been in the field for years. It is imaginative and sober, and its carefully worded predictions have stood the test of time. The paper won him a Rockefeller Fellowship to Pasadena to work with the *Drosophila* geneticist T.H. Morgan. There he met Linus Pauling with whom he published an important paper in 1940. That paper was an attack on the German theoretician P. Jordan who had advanced the idea that there exists a quantum-mechanical stabilizing interaction, operating preferentially between identical or near-identical molecules, which is important in biological processes such as the reproduction of genes. Pauling and Delbrück pointed out that interactions between molecules were now rather well understood and gave stability to two molecules of *complementary* structure in juxtaposition, rather than to two molecules with necessarily *identical* structures. Complementariness should be given primary

consideration in the discussion of the specific attraction between molecules and their enzymatic synthesis¹⁴. In 1937 the Cambridge geneticist and biochemist J.B.S. Haldane had made a similar suggestion: "We could conceive of a [copying] process [of the gene] analogous to the copying of a gramophone record by the intermediation of a negative, perhaps related to the original as an antibody is to an antigen"¹⁷. Schrödinger mentions neither of these important ideas.

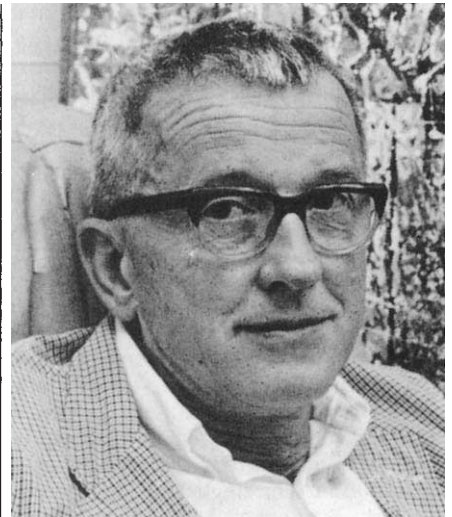
Schrödinger's last two chapters do contain his own thoughts on the nature of life. In "Order, Disorder and Entropy" he argues that "the living organism seems to be a macroscopic system which in part of its behaviour approaches to that purely mechanical (as contrasted with thermodynamical) conduct to which all systems tend, as the temperature approaches the absolute zero and the molecular disorder is removed". He comes to this strange conclusion on the ground that living systems do not come to thermodynamic equilibrium, defined as the state of maximum entropy. They avoid doing so, according to Schrödinger, by feeding on negative entropy. I suspect that Schrödinger got that idea from a lecture by Boltzmann on the Second Law, delivered before the Imperial Austrian Academy of Sciences in 1886:

Hence the general battle for existence of living organisms is not one for the basic substances — these substances are abundant in the air, in water and on the ground — also not for energy that every body contains abundantly, though unfortunately in a non-available form, but for entropy which becomes available by the transition of energy from the hot sun to the cold earth¹⁵.

Franz (later Sir Francis) Simon, then at Oxford, pointed out to Schrödinger that we do not live on $-T\Delta S$ alone, but on free energy¹. Schrödinger deals with that objection in the second edition of his book; he writes that he had realized the importance of free energy, but had regarded it as too difficult a term for his lay audience; to me this seems a strange argument, because the meaning of entropy is surely harder to grasp. Schrödinger's postscript did not satisfy Simon who pointed out to him in a letter that:

The reactions in the living body are only partly reversible and consequently heat is developed of which we have to get rid to the surroundings. With this irreversibly produced heat also flow small amounts (either + or -) of reversibly produced heat ($T\Delta S$), but they are quite insignificant and therefore cannot have the important effects on life processes which you assign to them¹.

In fact, it was known when Schrödinger wrote his book that the primary currency of chemical energy in the cells is ATP, and that the free energy stored in ATP is predominantly enthalpic. However, Schrödinger did not remove this misleading chapter from later editions.



Max Delbrück: predictions have stood the test of time.

The final chapter, "Is Life Based on the Laws of Physics?" reiterates and amplifies the central argument stated at the beginning of the book. According to Delbrück, Schrödinger writes, the gene is a molecule, but the bond energies in molecules are of the same order as the energy between atoms in solids, for example in crystals, where the same pattern is repeated periodically in three dimensions, and where there exists a continuity of chemical bonds extending over large distances. This leads him to the famous hypothesis that the gene is a linear one-dimensional crystal, but lacking a periodic repeat: an aperiodic crystal. A single such crystal, or a pair of them, direct the orderly process of life. Yet, according to Boltzmann's laws, their behaviour must be unpredictably erratic. Schrödinger concludes that:

We are faced with a mechanism entirely different from the probabilistic one of physics, one that cannot be reduced to the ordinary laws of physics, not on the ground that there is any 'new force' directing the behaviour of single atoms within an organism, but because the construction is different from any yet tested in the physical laboratory.

I wonder why Schrödinger did not adhere to Delbrück's much better formulation of "a polymeric entity that arises by the repetition of identical atomic structures". One could argue over the distinction between aperiodic and identical, but Delbrück could not have meant structures that are *completely* identical, since these could contain no information. Schrödinger does suggest that the genetic information might take the form of a linear code, analogous to the Morse code.

He argues that the nature of the gene allows only one general conclusion:

Living matter, while not eluding the laws of physics as established to date, is likely to involve other laws of physics hitherto unknown which, however, once they have been revealed, will form as integral a part of this science as the former.

Schrödinger is thus drawn to the same conclusion as Niels Bohr had been, apparently unknown to Schrödinger, twelve years earlier, and one that young physicists found equally inspiring.

Schrödinger next refers to a paper by Max Planck, "Dynamical and Statistical Laws". Dynamical laws control large-scale events such as the motions of the planets or of clocks. Clockworks function dynamically, because they are made of solids kept in shape by London-Heitler forces strong enough to elude disorderly heat motions at ordinary temperatures. An organism is like a clockwork in that it also hinges upon a solid: the aperiodic crystal forming the hereditary substance, largely withdrawn from the disorder of heat motion. The single cog of this clockwork is not of coarse human make, but is the finest piece ever achieved along the lines of the Lord's quantum mechanics. C.D. Darlington at Oxford had advised him that genes are likely to be protein molecules, as was then generally believed; Schrödinger quotes that, but does not mention that proteins are long chain polymers made up of some 20 different links that might form the kind of aperiodic patterns or linear code he had in mind. He must also have been unaware that the true chemical nature of that "finest piece" was actually published while he was writing his book. In January 1944 there appeared a paper by O.T. Avery, C.M. McLeod and M. McCarty which reported conclusive evidence that genes are made not of protein, but of DNA¹⁶. In the fullness of time, that discovery has led most scientists to the recognition that life can be explained on the basis of the existing laws of physics.

When I was invited to review the influence of *What is Life?* I accepted with the intention of doing honour to Schrödinger's memory. To my disappointment, a close study of his book and of the related literature has shown me that what was true in his book was not original, and most of what was original was known not to be true even when it was written. A.F. Huxley told me that even the charming contrast between the probable lifetime of a radioactive atom and a sparrow was misplaced. The incidence of death among a population of song birds hatched in any one Spring was known to follow exactly the same law as radioactive decay; for example, for the first ten years of its life, the probable lifetime of a robin is about one year, regardless of age. Older birds are too rare for statistics¹⁷. There is no reason to believe the lifetime of sparrows to be any more predictable than that of other birds. By contrast, my reading has raised even further my already great respect and admiration for Delbrück's analytical powers and scientific rigour, and for the prophetic and imaginative concepts formulated by J.B.S. Haldane and Linus Pauling, often long in advance of the rel-

evant discoveries. In retrospect, the chief merit of *What is Life?* is its popularization of the Timoféeff, Zimmer and Delbrück paper that would otherwise have remained unknown outside the circles of geneticists and radiation biologists.

The apparent contradictions between life and the statistical laws of physics can be resolved by invoking a science largely ignored by Schrödinger. That science is

"The apparent contradictions between life and the statistical laws of physics can be resolved by invoking a science largely ignored by Schrödinger. That science is chemistry."

chemistry. When Schrödinger wrote: "The regular course of events, governed by the laws of physics, is never the consequence of one well-ordered configuration of atoms, not unless that configuration repeats itself many times", he failed to realize that this is exactly how chemical catalysts work. Given a source of free energy, a well-ordered configuration of atoms in a single molecule of an enzyme catalyst can direct the formation of an ordered stereospecific compound at a rate of 10^3 – 10^5 molecules a second, thus creating order from disorder at the ultimate expense of solar energy. Haldane pointed this out in 1945, in his review of Schrödinger's book¹⁸.

Chemists could also have told him that there is no problem in explaining the stability of the large molecules of living matter that so much exercised him, because their bond energies range from 3eV upwards which corresponds to a half-life for each bond of at least 10^{30} years at room temperature. The difficulty resides in explaining how their aperiodic patterns are accurately reproduced in each generation. There is no mention of this central problem in Schrödinger's book; but its importance was recognized soon after Watson and Crick proposed their mechanism of DNA replication.

That replication is catalysed by an enzyme or system of enzymes that attach themselves to the end of the DNA double helix, unwind it, hold each parent strand rigidly in the conformation needed to catalyse the formation of a new chain link, move forward one step, catalyse the formation of the next link, and so on. The enzymes are large enough to arrest the random motions of the DNA chain, thus allowing an orderly process to take place in a single molecule without violating the known laws of physics^{19,20}. A system of enzymatic proof-reading and editing ensures that the error rate in DNA replication is between 10^{-9} and 10^{-10} , four to five orders of magnitude less than it would otherwise be.

Twenty five years after the Timoféeff,

Zimmer and Delbrück paper was published, H. Traut, then a graduate student working in Zimmer's laboratory, re-examined the evidence on which it was based and found the linear dose-response curve of Timoféeff to have been an artefact. He showed that the mutation rate of *Drosophila* germ cells varies widely at different stages of their development. If males are irradiated and then mated, the frequency of mutation among the offspring varies with the time that has elapsed between the two events, because the sperm that fertilizes a female five days after irradiation is at an earlier stage of development when it is irradiated than the sperm that fertilizes a female one day after irradiation. At all stages the dose-response curves are non-linear. Traut demonstrated that a linear response curve, similar to those observed by Timoféeff, is obtained by summing the different dose-response curves produced by matings during the first four days of irradiation²¹.

Zimmer comments:

This result removes one of the foundation-stones of the Green Pamphlet [as the Timoféeff, Zimmer & Delbrück paper became known]. Strangely enough, that does not seem to matter any more, for two reasons; (i) the concept of the gene and modern trends in genetic research as well as in radiation biology have changed considerably during thirty years, and (ii) the Green Pamphlet has served a useful purpose by helping to initiate these modern trends²². □

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