Thinking of Biology

What is Life? revisited

Almost 50 years ago, in February 1943, at the height of World War II, the quantum physicist Erwin Schrödinger delivered a series of lectures at Trinity College, Dublin, with the ambitious title "What is Life?". While most prominent theoretical physicists outside the Nazi ambit were working feverishly on the atom bomb, Schrödinger was speculating, instead, on the physical basis for life. He had just been "honoured," in his own words (in a press release Schrödinger wrote), "by the Nazi government with pensionless dismissal, without notice," from his academic chair in Austria (Moore 1989). He had then settled in Dublin as a professor at the Institute for Advanced Studies, newly founded by Eamon de Valera, the Irish premier who had a lifelong fascination with mathematics.

The lectures were a statutory responsibility. The intended audience was not limited to scientists. It was expected that most of Dublin's intellectual elite would attend. Perhaps because of that, Schrödinger turned to a favorite hobby—biology—rather than his professional work in physics. It appears that he intended the lectures to be published as a book even as he composed them, but it is also certain that he had no great faith in their putative importance (Moore 1989). Little did he know that the book would introduce a new concept to biology, that of a genetic code, and also be considered the most significant cause of an intellectual migration, from physics to biology, that would fully establish the emerging discipline of molecular biology.

Schrödinger's lectures were a serious attempt by a physicist to come to terms with the complex phenomena of life. He begins by asking, "How can events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?" His final answer is immediately stated: "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 those sciences" (Schrödinger 1967, p. 4–5). Physics would have to be explored further: only then would it explain the phenomena of life. But this answer was far from obvious. To reach it took the entire series of lectures.

Quantum mechanics and heredity

The biological problem that most fascinated Schrödinger was the nature of heredity: more than two-thirds of What is Life? is devoted to it. The traits of organisms are remarkably constant through generations. The deformed Hapsburg lip, for instance, could be traced back through all the surviving records of the Austrian royal family. Biologists had always been interested in heredity. Out of that interest emerged modern genetics. In the 1920s, R. A. Fisher, J. B. S. Haldane, and S. Wright had established the mathematical laws of the transmission of genes. Meanwhile, T. H. Morgan and his students, especially H. J. Muller, had established that genes were linearly arranged along a chromosome. It seemed as if the physical basis of heredity was almost solved. All one would need to study was the physical properties of chromosomes. Muller had already discovered some of these properties: radiation, for example, induced mutations.

Yet it was precisely the physical properties of genes—especially their stability—that Schrödinger found troubling. Classical (that is, pre-quantum) physics was of no help whatsoever. Organisms are complex physical systems: they consist of many atoms. Classical physics treats the behavior of bodies with many atoms statistically. To get exact laws, then, a very large number of atoms are necessary so that statistical fluctuations do not prove to be disruptive. Biological structures that obey exact laws, like genes, should therefore also consist of huge numbers of atoms. But, Schrödinger observed, this expectation is simply not true. Using an earlier calculation done by another physicist, Max Delbrück, Schrödinger observed that genes consisted of only a few million atoms, "much too small... to entail an orderly and lawful behavior according to statistical physics" (Schrödinger 1967, p. 32). Even this calculation turns out to have been an overestimate.

Thus classical physics cannot account for the stability of genes. The time had come to invoke quantum mechanics. Biology had returned to Schrödinger's intellectual home. He considered the gene as a quantum-mechanical system. The laws of quantum mechanics easily explained its stability, just as they explain the stability of all ordinary matter, such as rocks and crystals. Indeed, part of the power of quantum mechanics is that it is the first theory in physics that can account for such stability.

But quantum mechanics does more than just ensure the stability of genes. Genes, like any quantum mechanical system, can exist stably in many different states, which Schrödinger called "isomers," borrowing terminology from organic chemistry. Further, quantum mechanical systems can occasionally, at random, be transformed from one state to another. The process that allows for such transitions is known as tunneling. Schrödinger argued that such transitions in genes caused mutations. The different
isomers were the different alleles of a
gene. Thus a mutation was a random
event, and its result was as stable a
state as the original. From the point
of view of physics, genetics finally
began to make sense.

This model of the gene was not
new. It had been formulated by Del-
brück, who had made the transition
to biology a decade before (Timoféef-
Ressovsky et al. 1935). Schrödinger's
contribution, in this part of What is
Life?, was only to popularize the Del-
brück model, which had almost been
forgotten. He also gave a more intu-
tive description of the model than
Delbrück had ever presented. His con-
fidence in it was complete. "If the
Delbrück picture should fail," he
warned his audience, "we would have
to give up further attempts [to explain
genetics on the basis of quantum me-
chanics]" (Schrödinger 1967, p. 61).

The genetic code
The Delbrück model obviously could
explain the stability of the gene. But it
was essentially the model of any solid
and, from the point of view of quan-
tum mechanics, all solids are crystals.
They consist of periodic repeats of
some basic pattern. The trouble with
this model is that genes are not only
stably transmitted through reproduc-
tion, they also contain the informa-
tion for the construction and func-
tioning of organisms. They must,
therefore, have an immense variety.
How is this possible? Schrödinger's
answer was that the gene, though
solid, was yet aperiodic. Its repeated
subunits were not completely identi-
cal. Schrödinger elaborates this idea
in a remarkable passage. In it he
introduces, fully and clearly, the idea
of a genetic code:

It has often been asked how this tiny
speck of material, the nucleus of the
fertilized egg, could contain an elab-
orate code-script involving all the fu-
ture 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 pos-
sible ('isomeric') arrangements, suffi-
ciently large to embody a compli-
cated system of 'determinations'
within a small spatial boundary. In-
deed the number of atoms in such a
structure need not be very large to
produce an almost unlimited number
of possible arrangements. For illus-
tration, think of the Morse code. The
two different signs of dot and dash in
well-ordered groups of not more than
four allow thirty different specifi-
cations. Now, if you allowed yourself
the use of a third sign... and used groups
of not more than ten, you could form
8,872 different 'letters'; with five
signs and groups up to 25, the number
is 372,529,029,846,191,405. ... Of
course, in the actual case, by no means
'every' arrangement of the group of
atoms will represent a possible mole-
cule; moreover, it is not a question of
a code to be adopted arbitrarily, for
the code-script must itself be the operative
factor bringing about the develop-
ment. (Schrödinger 1967, p. 65-66)

Thus was born the idea of a genetic
code. The only earlier account that
even discusses the possibility of a
chemical code inside the hereditary
material is a letter of J. Miescher, the
discoverer of DNA, published in
1897 (Olby and Posner 1967). That
letter had no influence on genetics.
Some other biologists, such as D.
Wrinch (1936) and M. Bergmann and
C. Niemann (1937), had recognized
that the sequence of units in appar-
etly linear biological molecules
could determine their conformation
and function, but no one before
Schrödinger had made the critical
connection: that between a sequence
and a linear code.

New laws of physics
But what forces would maintain
DNA as an aperiodic solid (if that is
what it is)? Ordinary quantum me-
chanics would require periodicity. On
this question Schrödinger became
almost romantically radical: new prin-
ciples of physics would be needed.
"From Delbrück's general picture of
the hereditary substance," he
claimed, "it emerges that living mat-
ter, while not eluding the 'laws of
physics' as established up to date,
is likely to involve 'other laws of phys-
ics' hitherto unknown, which, how-
ever, once they have been revealed,
will form just as integral a part of this
science as the former (Schrödinger
1967, p. 73)." Thus there was noth-
ing vitalistic about the forces he en-
visioned.

The new laws of physics that
Schrödinger expected were not to be
new forces like electromagnetism or
gravity. They were to be new princi-
pies like the averaging techniques of
statistical mechanics, whereby the
bulk properties of bodies are obtained
as averages of the properties of the
particles inside them. Thus not only
would physics explain biology, but
biology would transform physics. Lit-
tle wonder, then, that a generation of
scientists found What is Life? most
provocative. Unfortunately, perhaps,
no such principles have emerged yet.
Biomolecules have just turned out to
be far larger and more complicated
than what Schrödinger had contem-
plated. As long chains are formed,
there are many more covalent bonds
than he had supposed. And order,
ultimately, relies heavily on hydrogen
bonds, about which Schrödinger
seems to have been unaware.

Beyond genetics, Schrödinger con-
fined his attention to the thermody-
namic properties of living organisms.
As they develop, organisms generate
order from their disordered environ-
ment. Thus they behave in a fashion
apparently contrary to that required
by the second law of thermodynam-
ics, which postulates an increase in
entropy or disorder. There is no par-
adox here, however, because living
organisms are not closed systems:
they interact and exchange matter
and energy with the environment.
The entropy of organism plus envi-
rronment continues to increase, as re-
quired by the second law, because the
entropy of the latter increases suffi-
ciently to overwhelm the decrease of
entropy in the former. Living organ-
isms thus feed on what Schrödinger
quixotically calls "negative entropy."
In the terminology that the modern
physicist Ilya Prigogine recently made
fashionable, Schrödinger can be con-
sidered to have given a brilliant qual-
itative account of a "dissipative struc-
ture," which is an organized open
system.

What is Life? concludes with what
Schrödinger admitted was his "neces-
sarily subjective" view of its philo-
sophical implications. In this epi-
logue, "On Determinism and Free
Will," which had not been included in
the public lectures, Schrödinger poses
the problem of free will. The observa-
tions that physics can ultimately ex-
plain all living phenomena and that
the laws of physics are (at least statis-
tically) deterministic seem inconsis-
tent with the freedom of the will that the mind experiences.

One possibility is that the mind is something different from matter. But the mind only arises in living things. Therefore, the mind must yet reside in matter. Schrödinger resolves this quandary by endorsing the Indian philosophical tradition of Vedanta, which links the mind, or individual consciousness (Atman), and the underlying universal reality (Brahman). Individual consciousness, from this point of view, is an unfortunate illusion: the goal of spiritual exercise is to get rid of this illusion and for the self to merge into the universal reality.

There is no duality of mind and matter at this fundamental level. Both arise as aberrations of the universal reality but, being independent aberrations, are not reducible to each other even when they arise together. Thus a completely physicalist account of living phenomena, one in which there are no traces of vitalism, is coupled to a completely mentalistic account of mind, one in which the laws governing matter have no role in the analysis of mind.

### The impact of Schrödinger’s book

The impact of *What is Life?* is hard to overestimate. It helped trigger an intellectual migration, especially from physics, that transformed biology: the molecular age had begun in earnest. Delbrück had pursued a similar course earlier, under the influence of another quantum physicist, Niels Bohr, but it was only after Schrödinger that the path from physics to biology became fashionable.

Without *What is Life?* many of the founders of molecular biology, such as Seymour Benzer and Maurice Wilkins, who were both trained as physicists, might never have entered biology (Yoxen 1979). The book attracted Gunther Stent and James Watson to the molecular basis of genetics (Yoxen 1979). Francis Crick, who was a physicist when he read *What is Life?*, found it exciting, although he says he would have entered biology in any case (Crick 1988). The distinguished physical chemist Cyril Hinshelwood recommended the book to all his students, even as he pursued purely chemical accounts of hereditary phenomena in bacteria, which he thought did not possess genes like those of higher organisms (Sarkar 1989).

### Recent assessments

Posterity, however, has not been kind to Schrödinger’s book. During the course of the Schrödinger centenary (Kilmister 1987), virtually all the commentators took Schrödinger to task for even suggesting new principles of physics. Linus Pauling and Max Perutz were even more critical. Pauling (1987) argued that Schrödinger should have stuck to the conventional form of thermodynamics, which requires the decrease of a quantity called the Gibbs free energy, of which negative entropy forms only a part. According to Pauling, not only did the book make no positive contribution but “by his discussion of ‘negative entropy’ in relation to life, [Schrödinger] made a negative contribution” (Pauling 1987, p. 229). Perutz (1987) has pointed out how little Schrödinger knew of the biology of his day; how he seemed not even to know that geneticists, including Delbrück, had switched from *Drosophila* to microorganisms and that the gene-enzyme relationship was emerging as a central problem in biology.

These negative assessments are excessively uncharitable. At the time Schrödinger was composing his lectures, it was not clear that the ordinary principles of statistical mechanics would suffice even to explain all macroscopic properties of inanimate matter. Indeed, it was in the early 1940s that the physicist Lars Onsager began to establish this fact. As one of the foremost theoretical physicists of his generation, and one with a strong interest in statistical mechanics, Schrödinger was certainly aware of the difficulties surrounding Onsager’s attempts. In that context, it was hardly irresponsible to speculate that new principles might well be necessary to explain what, from the point of view of physics, are the even more bizarre properties of living matter.

It is even stranger to blame or criticize Schrödinger for the use of the concept of negative entropy. The idea that living organisms converted information into negative entropy was introduced much earlier, in 1929, by Leo Szilard, another physicist who later made significant contributions to molecular biology (Szilard 1990). Moreover, Schrödinger’s formulation served as the foundation for yet another physicist, Leon Brillouin, to explore the connection between entropy and information. The recent work of Prigogine and his collaborators on dissipative structures is also an extension of Schrödinger’s ideas. Pauling’s strictures about free energy are formally correct, but it is the change in negative entropy (rather than free energy) that is truly curious about living processes and, for a popular audience, Schrödinger could hardly have done better than focus on it.

Perutz, too, is correct in noting that Schrödinger’s biology was not up-to-date, giving microorganisms short shrift. Delbrück, in particular, had begun to focus on the genetics of viruses, and *Escherichia coli* was emerging as an important research tool. However, in 1943, actual results from the genetics of microorganisms were not yet forthcoming and established genetics was still mostly the genetics of *Drosophila*. Schrödinger had apparently tried to be current by using Haldane’s prophetic *New Paths in Genetics* (1942) to prepare his lectures (Yoxen 1979). But Haldane gave microorganisms short shrift, and Schrödinger simply followed his example.

It is also true that Schrödinger does not mention the one gene–one enzyme hypothesis, which Haldane had formulated in 1937 (Haldane 1937) and G. W. Beadle and E. L. Tatum were beginning to establish. But in 1943 that hypothesis was far from certain, and, even as late as 1954, Haldane (1954) himself saw fit to warn against its universality. In such a context, Schrödinger’s silence hardly seems remarkable.

Even if all these criticisms of *What is Life?* were fair, it would still remain to Schrödinger’s credit that he had introduced the idea of the genetic code well before 1953, when the structure of DNA was discovered. Strangely, Pauling and Perutz, during the centenary, failed to note the idea’s significance, although it immediately generated some interesting, although speculative, biological work. Biochemists Kurt Stern (1947), P. C. Caldwell and C. N. Hishelwood
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