

Essay

Schrödinger's *What Is Life?* at 75Rob Phillips^{1,*}¹Division of Biology and Biological Engineering and Department of Physics, California Institute of Technology, Pasadena, California, USA*Correspondence: phillips@pboc.caltech.edu<https://doi.org/10.1016/j.cels.2021.05.013>

2019 marked the 75th anniversary of the publication of Erwin Schrödinger's *What Is Life?*, a short book described by Roger Penrose in his preface to a reprint of this classic as “among the most influential scientific writings of the 20th century.” In this article, I review the long argument made by Schrödinger as he mused on how the laws of physics could help us understand “the events in space and time which take place within the spatial boundary of a living organism.” Though Schrödinger's book is often hailed for its influence on some of the titans who founded molecular biology, this article takes a different tack. Instead of exploring the way the book touched biologists such as James Watson and Francis Crick, as well as its critical reception by others such as Linus Pauling and Max Perutz, I argue that Schrödinger's classic is a timeless manifesto, rather than a dated historical curiosity. *What Is Life?* is full of timely outlooks and approaches to understanding the mysterious living world that includes and surrounds us and can instead be viewed as a call to arms to tackle the great unanswered challenges in the study of living matter that remain for 21st century science.

Background: The author, his book, and its readers***Schrödinger and the circumstances of his public lectures***

Erwin Schrödinger is one of the luminaries of 20th century physics. His insights into the workings of the microscopic world were codified in the famed wave equation that bears his name and gave rise (among many other things) to the s, p, and d orbitals we all learn about in our first real encounter with this world in high-school chemistry. Schrödinger was born and raised in Austria, the only child of a highly intellectual family with a father deeply interested in botany, leaving Schrödinger himself with a sincere and enduring interest in the living world. In his *Autobiographical Sketches*, he recounts that because of discussions with his father, “I had virtually devoured *The Origin of Species*...Of course I soon became an ardent follower of Darwinism (and still am today)” (Schrödinger, 1992).

In the late 1930s after the *Anschluss*, Schrödinger had to flee the Nazis and turn his back on his professorship in Graz, Austria. Fortunately, Irish prime minister Éamon de Valera was in the process of establishing the Institute for Advanced Studies in Dublin, and it was there that the great physicist relocated. Later, speaking of his 17 years in Dublin, Schrödinger called them “the happiest years of my life,” and it was in the context of his life there that he offered the public

lectures that ultimately became the book we celebrate here (see Figure 1 for the cover page of the 1944 edition). To get a deeper sense of the impressive intellect that Schrödinger brought to bear on topics far and wide such as his gift for languages (including English, Spanish, and ancient Greek), the breadth of his accomplishments in physics and his personal lifestyle, there are several excellent sources (Dronamraju, 1999; Gribbin, 2013; Moore, 2015). Noted physicist Max Born's autobiography gives us an impression of the regard Schrödinger commanded among his intellectual peers: “His private life seemed strange to bourgeois people like ourselves. But all this does not matter. He was a most lovable person, independent, amusing, temperamental, kind and generous, and he had a most perfect and efficient brain” (Born, 2014).

The book's mission: “Accounting” for life

Schrödinger's *What Is Life?* constitutes a long argument in which he sets himself the task of nothing less than the search for “unified, all-embracing knowledge” to describe the natural phenomenon we refer to as life. In the section entitled “The General Character and Purpose of the Investigation,” he articulates his quest for universal knowledge more precisely by asking the oft-quoted question “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” (Schrödinger, 1992)? And answering that question is what the entirety of the long argument that follows is devoted to accomplishing. He asserts that the intellectual ledger sheet was not yet balanced, with the data outpacing corresponding conceptual understanding that “accounts” for them, words that remain true to this day. Indeed, to really put forth a critical reading of Schrödinger's text, we need to understand what he means by the word “account,” a point that was overlooked by many of his most ardent critics and which serves as the first key point of this essay.

Impact on the founders of modern biology

Most contemporary discussions of Schrödinger's book focus not on its content but on its influence on a generation of biologists. As a result, it seems important to touch briefly on that story before turning to the main argument that Schrödinger's call for a physics of the living world remains valid today. Nearly a decade before the publication of the structure of DNA by Watson and Crick, Schrödinger was already thinking about what came to be known as the coding problem. As Horace Freeland Judson tells us in his classic history of modern biology, *The Eighth Day of Creation* (Judson, 1996): “The earliest mention of coding that counts was Erwin Schrödinger's, in 1944 in ‘What is Life?’...The fascination



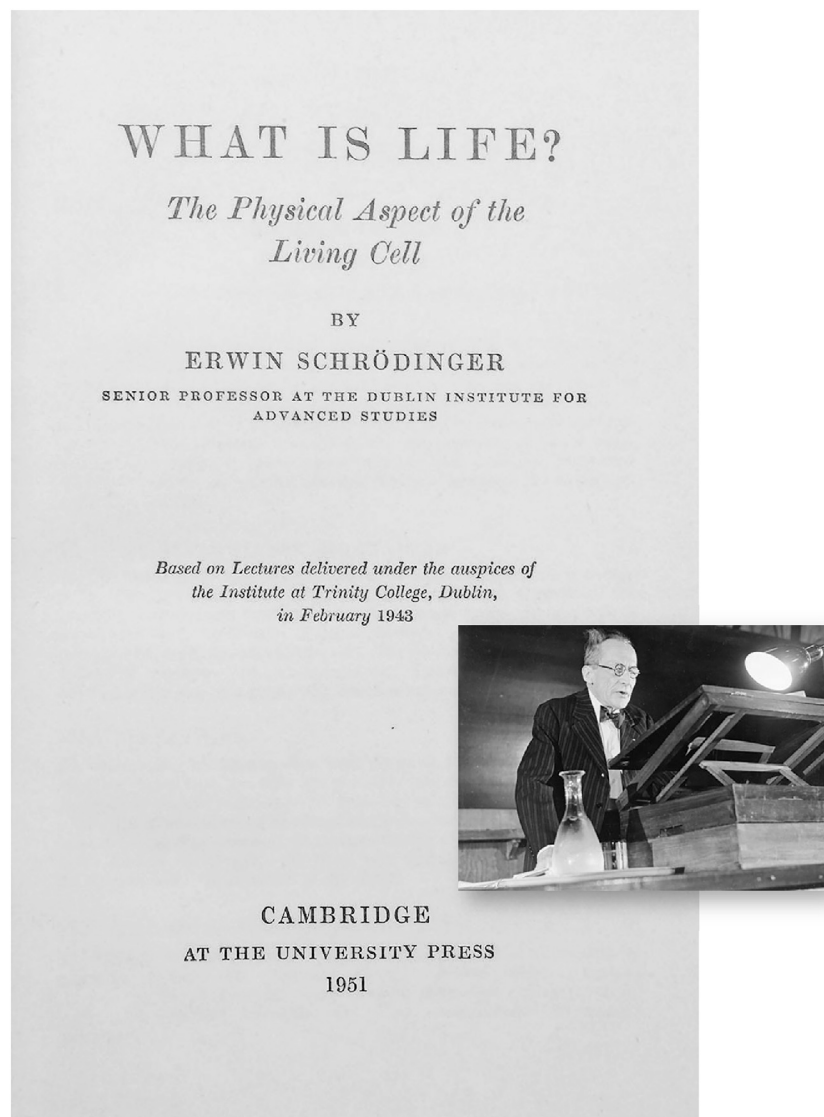


Figure 1. The 1944 edition of Erwin Schrödinger's *What Is Life?*, published by Cambridge University Press

The book resulted from a series of public lectures offered by Schrödinger in Dublin in 1943.

of the book lay in the clarity with which Schrödinger approached the gene not as an algebraic unit but as a physical substance that had to be almost perfectly stable and yet express immense variety." The influence of Schrödinger's book on some of the founders of modern biology is evidenced by Figure 2, which shows a letter from the young Francis Crick to the elderly master.

With the historical preliminaries behind us, we turn instead to a different question: to what extent is Schrödinger's classic relevant to the practice of biology and physics here and now? I

argue that the vast majority of what Schrödinger had to say remains unfinished business. This makes it an opportune time at this three-quarters of a century milestone to ask what would it look like for the entirety of modern science, with no allegiance to any particular sub-discipline within science, to revisit the question of the "physical aspect of the living cell"? The remainder of the essay centers on two key points: (1) Schrödinger argues that the part of the natural world we refer to as life needs to be "accounted for" in physical terms and (2) the quest to do such accounting

will lead to new physics, not only helping us make sense of life, but also enriching physics itself.

The meaning of "accounting for the living organism"

Schrödinger's charge was to find out how the actions within the walls of a living organism can "be accounted for by physics and chemistry." When he uses the words "account for," what I think he had in mind was the idea that our understanding of some phenomenon of interest can be seen as resulting from an appeal to some underlying principle—that that appeal is formulated in mathematical language in such a way that observed phenomena are seen as quantitative consequences of these underlying principles and that the resulting insights make it possible to make statements about phenomena not yet seen or measurements not yet made.

"Accounting for" inanimate matter

A fitting analogy for what Schrödinger meant when talking of "accounting for" some class of phenomenon "by physics and chemistry" is provided by his own work, for which he is so deservedly famous. In the mid- and late-19th century, there was an explosion in our *factual* knowledge about the light given off by and absorbed by different chemical elements in the form of their atomic spectra, as shown in Figure 3. Just as with our current proliferation of gene and protein names and the burdensome nomenclature for the pathways that connect them, the era of factual discovery in atomic spectra saw a proliferation of fascinating and complicated spectral nomenclature with concepts such as the D-line of Na and the different series such as the Balmer, Lyman, Brackett and Paschen series that are observed in the H spectrum (for a sense of the enormity of the factual diversity of these lines see Harrison, 1939). But what set the wavelength of absorbed or emitted light for a given element, or the number of spectral lines in a series?

Understanding in physics demands that factual knowledge based on experiments be complemented by *conceptual* knowledge. Precisely the same kind of unified, all-embracing knowledge that Schrödinger was speaking of in *What Is Life?* was earlier needed for thinking about the huge diversity of special cases

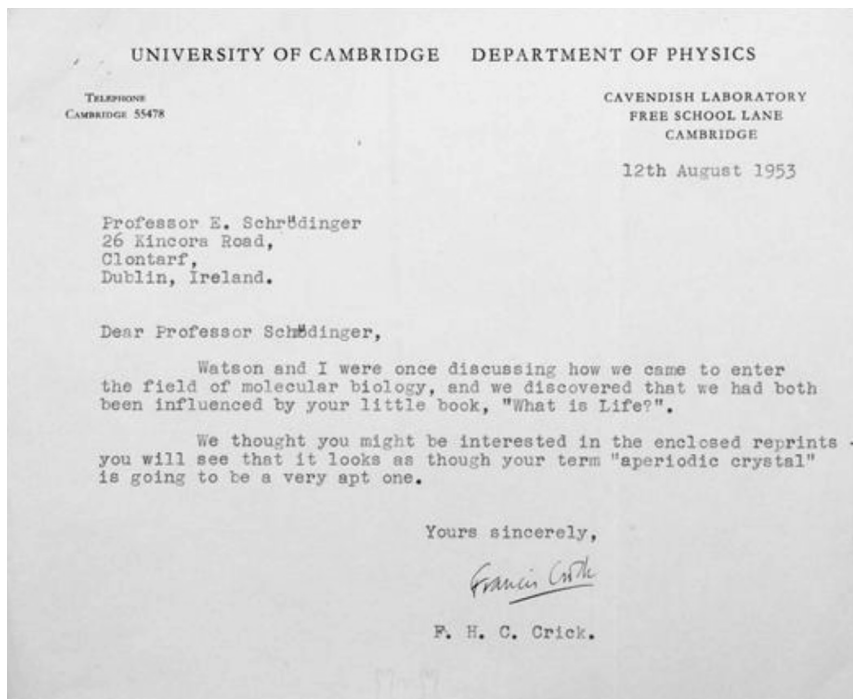


Figure 2. Letter from Crick to Schrödinger openly acknowledging the importance of *What Is Life?* to his career

found in atomic spectra (for an enlightening description of the history of the study of atomic spectra, see Mehra and Rechenberg, 1982). Nearly a century of struggle followed the discovery and experimental characterization of spectral lines as evidenced by the words of Max Planck in 1902: “If the question concerning the nature of white light may thus be regarded as being solved, the answer to a closely related but no less important question - the question concerning the nature of light of the spectral lines - seems to belong among the most difficult and complicated problems which have ever been posed in optics or electro-dynamics.” (Planck, 1902) One outcome of these struggles (see Figure 3) was the discovery of empirical formulae that gave a phenomenological mathematical description of the measured wavelengths of various spectral lines seen in Figure 3A of the form,

$$\frac{1}{\lambda} = R \left(\frac{1}{p^2} - \frac{1}{n^2} \right), \quad (\text{Equation 1})$$

where λ is the wavelength of the spectral line in question, R is a phenomenological parameter known as the Rydberg constant, later “accounted for”

by physical understanding, and p and n are integers.

To account for such phenomenological understanding requires us to construct theories that explain why spectral lines are described by such a formula and what determines the phenomenological constant R . Niels Bohr’s theory of the hydrogen atom gave a first tentative conceptual success where he posited that the electron orbits are restricted to certain quantized values with energies,

$$E_n = - \frac{Z^2 m e^4}{8 h^2 \epsilon_0^2 n^2}, \quad (\text{Equation 2})$$

with m the mass of the electron, e the elementary charge of the electron, h the symbol for Planck’s constant, and ϵ_0 the permittivity of free space. Here, the steps toward accounting take the form of the stunning realization that the empirical Rydberg constant can in fact be written as

$$R = \frac{m e^4}{8 h^3 c \epsilon_0^2} \approx 1.1 \times 10^7 \text{ m}^{-1}. \quad (\text{Equation 3})$$

Erwin Schrödinger’s great atomic triumph, shown in Figure 3, was the insight

that he could interpret the discrete energy levels of atomic systems in much - the same way that we interpret the musical notes from a guitar string or an organ pipe using wave equations.

Our digression into the niceties of how theoretical understanding “accounted” for the many complexities of spectral lines and so much more about the complicated microscopic world is meant to serve as an invitation to the kind of physical frameworks that Schrödinger might have had in mind when discussing living matter and using the words to “account for” a given phenomenon.

Accounting for living matter: From thermal energy to shot noise

Though Schrödinger clearly left the door open for quantum insights into the phenomenon of life, much of his thinking centers on what is now known as statistical physics. In the 19th century, statistical physics arose in response to other phenomena demanding his type of accounting. By then, mechanics had dominated as an explanatory framework for more than a century, from Newton’s 1687 presentation of his *System of the World*, until the middle of the 19th century when questions about the nature of heat began to take center stage (Brush, 1986; Klein, 1973). We can use Schrödinger’s language in that context as: how can our experience of temperature and heat be accounted for by the mechanical motions of material particles? The quest to answer that question took the better part of a century, culminating in the twin edifices of statistical physics and thermodynamics, but also leaving in its wake unresolved problems such as the specific heats of crystalline solids that would have to await the quantum theory for their proper resolution (Pais, 1979).

Statistical physics was clearly much on Schrödinger’s mind in his Dublin years as evidenced not only by *What Is Life?*, which is full of deep insights into the subject that can be read with great profit with no reference to biology whatsoever, but also by his 1946 book, *Statistical Thermodynamics*, still a masterful treatise that one can learn from to this day. Schrödinger was schooled in the Austrian tradition of Ludwig Boltzmann’s statistical physics, having only missed having one of the great founders (along with Maxwell and Gibbs) of statistical mechanics as a professor by a year or two due to Boltzmann’s tragic suicide.

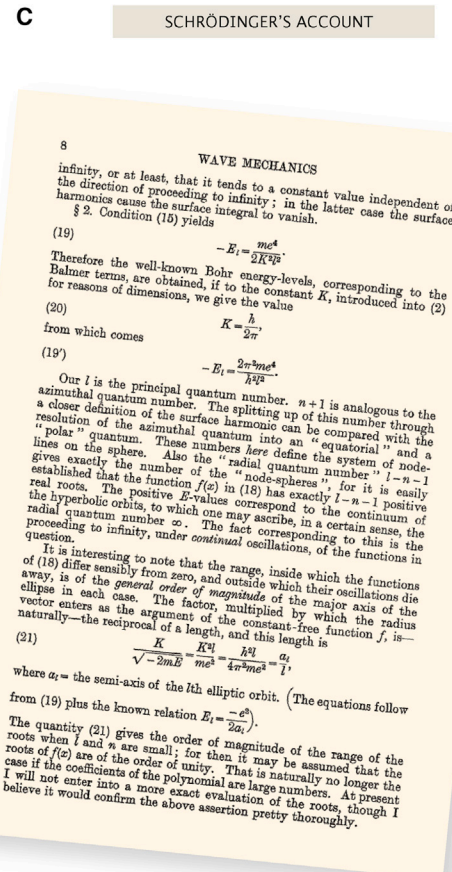
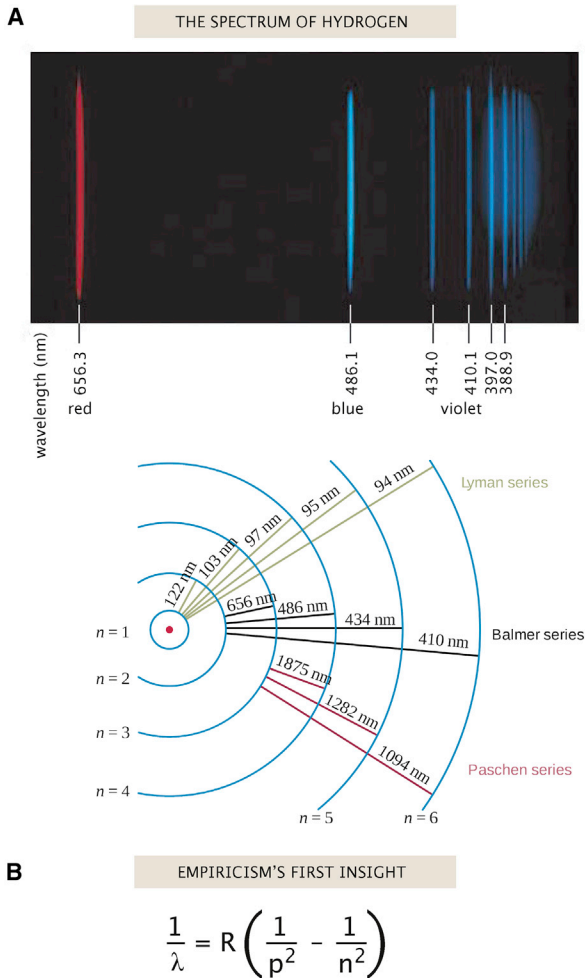


Figure 3. Accounting for the spectrum of hydrogen

(A) The spectrum of hydrogen with the wavelengths of various spectral lines reported in nm. (B) The Balmer formula for the wavelengths of the spectral lines featuring the Rydberg constant, R . (C) Page from the English translation of Schrödinger's paper on wave mechanics in which he shows that the equation that now bears his name amazingly gives rise to precisely the energy levels found earlier by Niels Bohr that explain the spectrum of hydrogen.

But this did not stop Schrödinger from being steeped in the tradition of statistical physics that ultimately became central not only to our scientific understanding of classical physics, but also to the way we view the quantum world he helped uncover. For Schrödinger as announced in his *Autobiographical Sketches*, “no perception in physics has ever seemed more important to me than that of Boltzmann—despite Planck and Einstein,” a resounding testament to the statistical physics sensibilities he brought to the table in his thinking about the nature of life, and the shortcomings of which led to his belief in the ultimate need for “new physics” to account for living matter (Schrödinger, 1992).

As an introduction to the shortcomings of the physics of Schrödinger's time to ac-

count for the living organism, Chapter 1 of *What Is Life?* introduces “The Classical Physicist's Approach to the Subject.” Schrödinger reminds us that statistical mechanics is the central conceptual framework used until that time to interpret the collective properties of matter. To that end, he begins by providing a beautiful and compelling introduction to the key ideas of statistical physics. Why? Because, as he points out, “it is in relation to the statistical point of view that the structure of the vital parts of living organisms differs so entirely from that of any piece of matter that we physicists and chemists have ever handled physically in our laboratories or mentally at our writing desks” (Schrödinger, 1992). This idea of what Schrödinger dubs a “difference in statistical structure” between conven-

tional and living matter is a theme that permeates the entirety of his short book. The first chapter thus lays the general groundwork for what follows by giving a highly simplified but profound view of statistical physics. There, he raises many of the themes that dominate modern biology including the roles played by stochastic effects, small numbers, adaptation, accuracy, and noise in the reproducible processes of cells and organisms.

In Chapters 2–5, he brings the general arguments of Chapter 1 to bear on his first big specific question: how is genetic information so stably passed from one generation to the next, despite how few atoms are implicated in the gene (as we will discuss in the next section)? Indeed, Schrödinger argues that the stability of the genetic material is inconsistent with

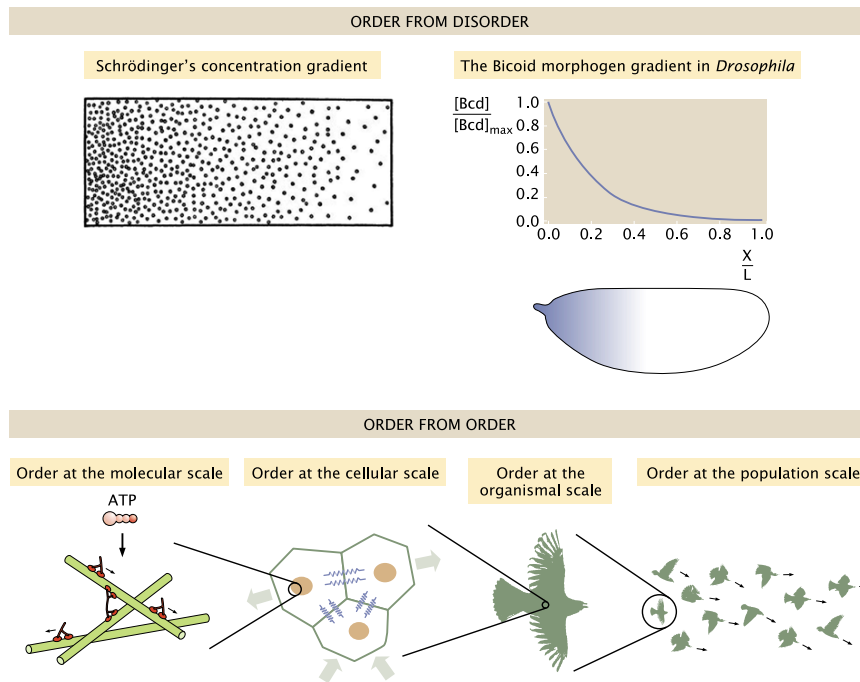


Figure 4. Schrödinger's order from disorder and order from order

Top panel: Schrödinger illustrated the way that strictly random motions of atoms or molecules could give rise to reproducible patterns of concentration (left). Modern developmental biology has borne that out in the form of morphogen gradients such as the gradient of the transcription factor Bicoid in the fly embryo shown here schematically beneath the graph. The length (L) of the embryo is plotted in dimensionless units x/L . The profile of Bicoid can be thought of as emerging from the “disordered” processes of diffusion and protein degradation. Bottom panel: the expenditure of energy at very small scales in the form of ATP hydrolysis leads to order at the cellular scale, the organismal scale and even the population scale.

the then-known laws of statistical physics. Though it is mind-boggling to consider, one could say that in some sense biological information is more stable than is the Earth itself. In the 50 million or so years since the Indian subcontinent collided with Asia, 8,000 m mountains have been thrust up from the Earth, while at the same time, the *Hox* genes that confer body plans in animals from flies to humans have passed from one generation to the next such that the family resemblances are completely evident when we compare sequences from different organisms. By focusing on the nature of the hereditary molecule now known to be DNA, Schrödinger foreshadowed the agenda for the DNA-centric perspective that colors much of modern biological investigation.

After concluding that the stability of genetic information leaves puzzles for the physics of his (and our) day, Schrödinger then turns to another set of biological phenomena that defied the physics of his time. Here, he focuses on what in modern

guise we might call the physico-chemical basis of the self-organization of living matter. One of the most disturbing of human tendencies is how we all become accustomed to the wonders around us, whether in our science or in our lives. One example that I find remarkable is seen on transatlantic flights where, as we pass over the glaciers of Greenland, nearly all passengers have their shades closed without even a thought of what lies below. I might recast Schrödinger's question about the physico-chemical basis of the organization of living cells thus: how do the elements of the periodic table, when sculpted by the consumption of energy at the nanometer scale through ATP hydrolysis, come together and form remarkable structures such as the insect eye or the dynamic and constantly renewing outer segment of animal photoreceptors? These amazing rhodopsin-filled structures are a reminder to do the scientific equivalent of opening the shades over Greenland and marvel at living cells as collections of atoms from the periodic ta-

ble that produce “endless forms most beautiful and most wonderful.”

Let's look a little more closely at the way that Schrödinger examined the capacity of statistical physics to account (or not) for living matter. As a first example of the statistical structure of classical physics, he tackles the question of paramagnetism (how the tiny individual magnets of single atoms conspire to give rise to the macroscopic phenomenon of magnetism, and how it depends upon temperature). The magnetic phenomenon results from a competition between the energy advantage that comes from aligning spins with an applied magnetic field and the entropy that comes from those spins adopting random orientations. The key point is the recognition that the thermal energy scale, $k_B T \approx 4.1$ pN nm, as Schrödinger points out, is the natural energy scale that presides over the atomic and molecular world (and the molecules of the living world can only find immunity from this energy scale by investing some other energy such as ATP hydrolysis to avoid it—see the bottom panel of Figure 4).

With the “order from disorder” exhibited by magnetic materials in hand, he then proceeds to a description of Brownian motion. Schrödinger's little four-page discussion of diffusion culminating in the diffusion equation itself is as perfect a description of the subject as I have ever seen. The important point of this discussion is to illustrate the lawful mathematical precision that emerges from the apparent lawlessness of the flips of a coin as each molecule randomly chooses to move left or right, up or down. Speaking of the jostling of these Brownian particles, Schrödinger poetically muses: “Their movements are determined by the thermic whims of the surrounding medium; they have no choice. If they had some locomotion of their own, they might nevertheless succeed in getting from one place to another—but with some difficulty, since the heat motion tosses them like a small boat in a rough sea.” Again, the statistical structure of classical physics reveals that ordered states with the mathematical precision of an exponential function such as the concentration gradient shown in Figure 4 in fact emerge from the second law of thermodynamics which tells us that systems evolve toward states of maximum

entropy, yielding a kind of order from disorder. Turing's paper showing an even more subtle and beautiful example of order from disorder was still a decade in the future (Turing, 1952).

Once these foundations have been laid, Schrödinger starts honing in on biological phenomena by considering the "limits of accuracy of measuring," the insight being that there are limits to such measurement because of the natural fluctuations of the measuring device itself, a phenomenon perhaps even more important in living organisms than in the experimenter's apparatus. Indeed, in my view, in this section, Schrödinger foreshadowed one of the most important themes of modern physical biology, namely, how living organisms defy the strictures of equilibrium physics. These questions arise in settings ranging from the origins of high-fidelity polymerization and the emergence of the concept of kinetic proofreading (Hopfield, 1974; Ninio, 1975) to the measurement of concentration differences by cells performing chemotaxis (Berg and Purcell, 1977) to the emergence of herds with orientational order in apparent defiance of fundamental physical theorems (Toner, 2018). The topic of fidelity in biological polymerization was also brilliantly undertaken by Linus Pauling (Pauling, 1957), but from a molecular perspective rather than the conceptual point of view adopted by Schrödinger.

Schrödinger starts his discussion on the limits of accuracy of measuring with an analysis of the kinds of torsional balance apparatus used by Cavendish (gravity) and Coulomb (electrostatics) to measure the classic inverse-square laws. His point is that as the apparatus gets smaller and smaller, the deflections induced by the forces of interest will be comparable in magnitude to those induced by thermal motion. Questions of biological accuracy and precision have now become a centerpiece of rigorous thinking in modern biology in the form of the Berg-Purcell limit, but more generally in the context of how well living organisms can sense their environments, whether in the context of hearing or seeing, or in the detection of chemical messengers (Bialek, 2012). Schrödinger (1992) himself understood precisely the physics question in play, noting:

The uncontrollable effect of the heat motion competes with the effect of the force to be measured

and makes the single deflection observed insignificant. You have to multiply observations, in order to eliminate the effect of the Brownian movement of your instrument. This example is, I think, particularly illuminating in our present investigation. For our organs of sense, after all, are a kind of instrument. We can see how useless they would be if they became too sensitive.

But this is all more than pretty words. Schrödinger wants to describe these physical challenges to the living organism quantitatively. He notes the monotonous repetition of this same statistical principle in the inorganic world but wants his listeners and readers to know that there is a simple mathematical law, the "so-called \sqrt{n} law," that tells us the size of the fluctuations to be expected in a system containing n atoms or molecules. Schrödinger summarizes that law as: "The laws of physics and physical chemistry are inaccurate within a probable relative error of the order of $1/\sqrt{n}$, where n is the number of molecules that co-operate to bring about the law - to produce its validity with such regions of space or time (or both) that matter, for some considerations or for some particular experiment" (Schrödinger, 1992). These ideas are central to modern biological enquiry. For example, when photosynthetic bacteria divide, they have to carry with them copies of a photosynthetic organelle known as the carboxysome, with only a few (3–6) copies per cell. During the division process, they have special machinery to prevent these unwanted $1/\sqrt{n}$ partitioning errors (Savage et al., 2010). By way of contrast, partitioning errors in transcription factors are a demonstrable part of the reason for noisy gene expression (Rosenfeld et al., 2005; Rosenfeld et al., 2006). And yet, and here is the crux of the whole book, "The classical physicist's expectation, far from being trivial, is wrong" (Schrödinger, 1992). As seen by the carboxysome example, living organisms have found ways to insulate themselves from the all-important \sqrt{n} law and many of the other strictures of equilibrium statistical physics.

As I will elaborate on below, one way to think of that "wrongness" is summarized in the bottom panel of Figure 4, which hints at the need for a statistical physics

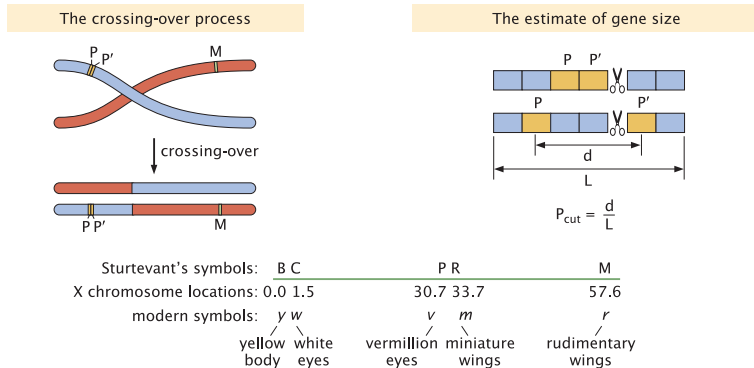
of the phenomena that emerge when energy is invested to keep those systems out of equilibrium, an enterprise that has been undertaken to great effect in recent decades (for a flavor of this new physics, see Seifert, 2012). To further elaborate on why the classical physicist's expectation is wrong, let's revisit Schrödinger's quantitative analysis of the question of the stability of the genetic information.

Fermi problems in Schrödinger style

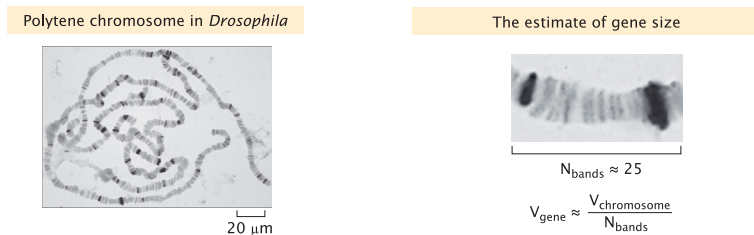
Numbers sharpen our questions. Schrödinger appreciated this sharpness and used quantitative estimates as a key part of his arguments. In the world of physics, numerical estimates to describe some phenomenon of interest are sometimes known as Fermi problems and are a model for the power of order-of-magnitude reasoning to clarify both our questions and our thinking in response to those questions. Their name refers to a style of thinking brought to an art form by Italo-American physicist Enrico Fermi, who could estimate his way to numerical answers to questions ranging from the number of piano tuners in a big American city, to the heat loss in our homes if we forget to install storm windows, to the yield of the atomic explosion in the Trinity Test of 1945. Fermi brought this same approach (Mahajan 2010) to critical questions in the science challenges he faced in his professional life as a physicist. For example, the design of the first successful nuclear reactor—built upon a string of systematic preliminary studies, each characterized by numerical estimates on topics such as neutron diffusion—led Fermi to predict the precise moment that the Stagg Field nuclear reactor would reach a self-sustained nuclear reaction (Schwartz 2017).

Schrödinger's book draws from the same Fermi-problem inkwell. In fact, Schrödinger's short manifesto gives perhaps the best example of a physicist working through Fermi problems in plain view that I have seen in written form. Over and over, Schrödinger poses questions of the form: what sets the scale of X ?, the quintessential framing of questions in order-of-magnitude thinking. Examples include what sets the relative scale of organisms and atoms, what is the size of a gene, and how much energy

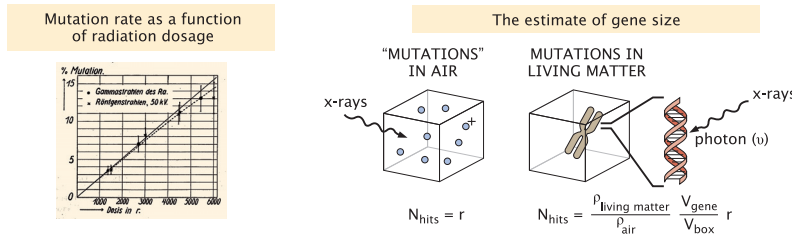
ESTIMATE #1: CROSSING-OVER FREQUENCIES



ESTIMATE #2: CHROMOSOMAL BANDING PATTERNS



ESTIMATE #3: RADIATION-INDUCED MUTATION RATE



ESTIMATE #4: MODERN GENOME SCIENCE

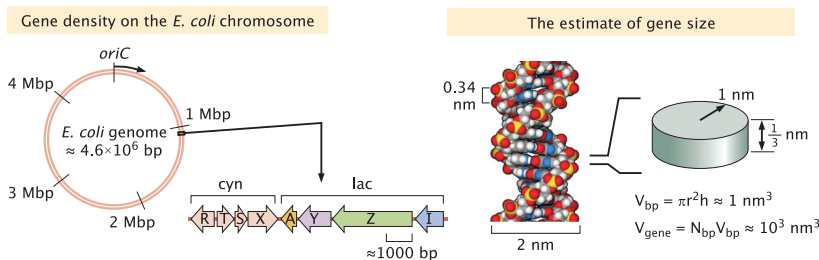


Figure 5. The size of a gene

The first estimate exploited the beautiful insights into mapping genes on chromosomes (originally in *Drosophila*) to figure out the mean spacing of genes. Given the gene number and the size of chromosomes, this approach would yield helpful insights. Schrödinger's second estimate uses banding patterns on chromosomes on the mistaken assumption that each band is a gene. The Delbrück estimate was based on the mutation rate induced by X-rays. A modern estimate uses the number of base pairs in a gene and the very useful rule that the volume of a base pair is 1 nm^3 . For more details of the paper of Timoféeff-Ressovsky, Zimmer, and Delbrück that measured the data shown on mutation rate and radiation dosage, see the book *Creating a Physical Biology*, which includes its translation (Sloan and Fogel, 2011).

is needed to maintain the stability of the gene?

Having laid down his statistical mechanical and order-of-magnitude thinking

foundations, Schrödinger was now prepared to take up the question of the size of a gene. His musing on this question is motivated by the statistical structure of

classical physics and his interest in how biological systems deal with the \sqrt{n} law introduced above. His argument is that if the number of atoms associated with a gene is small, then the natural fluctuations of such systems would impact the stability of genetic information. Concretely, he wonders, how many atoms are associated with a gene and if that number is small in the sense of the \sqrt{n} law, then how do these genes safeguard themselves from the inevitable statistical fluctuations present in any collection of atoms?

On the physical dimensions of genes

To examine the question of the size of a gene, Schrödinger performs several different estimates that are illustrated in Figure 5. Note the painstaking and often misguided detective work involved in answering such a deep question as the size of the gene before it was even widely accepted that DNA is the genetic material. Schrödinger begins with two entirely independent estimates of the size of the gene. The first, shown in Figure 5A builds on the subsection of his book entitled "Crossing-over. Location of properties", in which he explains how maps like the classic case for *Drosophila* of Alfred Sturtevant are discovered. As seen in the figure, when there is a crossing over event, we can ask the frequency with which two genes end up on the same strand together. The more likely that occurrence, the closer those two genes are on the chromosome and from these frequencies an actual map of gene positions on the chromosome can be divined. Given one of these maps of a chromosome, Schrödinger proposes a strictly order-of-magnitude upper bound on the size of a gene based on the size of a chromosome and the number of "properties" (i.e., genes) per each chromosome. As he notes, the estimate provides a bound, because at the time of his writing, the entirety of the genes on a chromosome had not yet been mapped. The concept of the estimate is reasonable as is indicated for a bacterial genome in Figure 5D. The second such estimate is a very clever (though "wrong") idea of using the banded patterns of chromosomes as a measure of gene size. As seen in Figure 5B, if we consider the 23 chromosomes (Schrödinger refers to 24 pairs of chromosomes, true for chimps, but not humans) with their banding patterns, this

estimate will say that the size of a gene is much larger than we know to be true.

He really hits his stride when considering a third estimate of the size of a gene as seen in Figure 5C. This is the point in the story where Schrödinger's reports on the work of Max Delbrück and co-workers, inspiring Perutz's remark, "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" (Perutz, 1987). As seen in the figure, experiments on ionization of gases allowed for a measure of radiation intensity that could then be directly translated into a tool for examining radiation damage in DNA. By measuring the radiation-induced mutation rate, an estimate for the size of a gene could be made leading to the idea that a gene involves roughly 1,000 atoms. Our modern understanding of the DNA double helix tells us that a base has $\text{few} \times 10$ atoms, meaning that a typical thousand nucleotide bacterial gene would involve on the order of $\text{few} \times 10^4$ atoms, a bit more than a factor of 10 larger than Schrödinger's estimate. Though his estimate is too low for the size of an entire gene and a little too large for the size of a base pair, it is an impressive use of indirect reasoning to arrive at molecular dimensions that conjures images of the way Benjamin Franklin, Lord Rayleigh, Agnes Pockels, and Irving Langmuir attacked the question of the molecular dimensions of lipid molecules indirectly by looking at the spreading of oil on water (Langmuir, 1917; Tanford, 2004).

The outcome of these arguments leaves Schrödinger (1992) with a mystery: "We are now seriously faced with the question: How can we, from the point of view of statistical physics, reconcile the facts that the gene structure seems to involve only a comparatively small number of atoms (of the order of 1,000 and possibly much less), and that nevertheless it displays a most regular and lawful activity—with a durability or permanence that borders upon the miraculous"? In examining this question, we have to put ourselves in the mindset of Schrödinger who is once again asking us from the perspective of what it means for *physics* (not biology) to account for these phenomena. Schrödinger then goes farther

by noting, "Thus we have come to the conclusion that an organism and all the biologically relevant processes that it experiences must have an extremely 'many-atomic' structure and must be safeguarded against haphazard, 'single-atomic' events attaining too great an importance" (Schrödinger, 1992). All of this kind of "what sets the scale of X" thinking brought Schrödinger to precisely the same place that was arrived at 30 years later in a different way by John Hopfield and Jacques Ninio when they presented a theory of just the kind of "safeguarding" called for in *What Is Life?* and that now goes under the name of kinetic proofreading (Hopfield, 1974; Ninio, 1975).

The biological frontiers of physics: New laws to be expected in the organism

Having made his arguments about the shortcomings of the statistical physics of his time to account for the stability of living matter, Schrödinger closes the book with some higher-level thinking on the implications of living matter for the future of physics. In their great book *The Evolution of Physics*, Albert Einstein and Leopold Infeld make it very clear how physics has repeatedly been driven forward by new experimental measurements (think Faraday and electromagnetic induction) that demand the emergence of new concepts (Einstein and Infeld, 1938). At the beginning of the 19th century, the concept of entropy, one of the foundational ideas of modern science, had not even been conceived or defined, but an increasingly sophisticated experimental program revealing the character of temperature and heat demanded it. Similarly, although the idea of "field theory" was implicit in the development of continuum mechanics by great thinkers such as Euler, it would have to await the labors of Faraday, Maxwell, and others before it took the proportions that would lead Einstein and Infeld to say, "A new concept appears in physics, the most important invention since Newton's time: the field. It needed great scientific imagination to realize that it is not the charges nor the particles, but the field in the space between the charges and the particles which is essential for the description of physical phenomena" (Einstein and Infeld, 1938). The question is: to deliver on Schrö-

dinger's call to "account for" the phenomena of life, what new experiments and concepts do expanding our domain of physical enquiry into the realm of the living demand?

My understanding of Schrödinger's book is that he is arguing that, just as the phenomena of heat and electro-dynamics forced upon us a myriad of new concepts such as temperature, entropy, the electric field, and radiation pressure, the phenomena of the living world similarly demands the continued evolution of physics through new concepts. In his section on "New Laws to Be Expected in the Organism," Schrödinger (1992) reveals his hand:

What I wish to make clear in this last chapter is, in short, that from all we have learnt about the structure of living matter, we must be prepared to find it working in a manner that cannot be reduced to the ordinary laws of physics. And that not on the ground that there is any "new force" or what not, directing the behavior of the single atoms within a living organism, but because the construction is different from anything we have yet tested in the physical laboratory.

Indeed, would anyone be surprised by the idea that, as we subject new classes of phenomena to quantitative scrutiny in the physical laboratory yet again, as has been true every century since the days of Tycho Brahe, new concepts will be demanded of us?

Schrödinger (1992) makes this point beautifully through a colorful analogy for thinking about how the elements of the periodic table can be exploited to totally different ends in living matter.

To put it crudely, an engineer, familiar with heat engines only, will, after inspecting the construction of an electric motor, be prepared to find it working along principles which he does not yet understand. He finds the copper familiar to him in kettles used here in the form of long wires wound in coils; the iron familiar to him in levers and bars and steam cylinders here filling the interior of those coils of copper wire. He will be

convinced that it is the same copper and the same iron, subject to the same laws of Nature, and he is right in that. The difference in construction is enough to prepare him for an entirely different way of functioning. He will not suspect that an electric motor is driven by a ghost because it is set spinning by the turn of a switch, without boiler and steam.

Schrödinger thus concludes, “it needs no poetical imagination but only clear and sober scientific reflection to recognize that we are here obviously faced with events whose regular and lawful unfolding is guided by a ‘mechanism’ entirely different from the ‘probability mechanism’ of physics” (Schrödinger, 1992). One category of “new laws” that might prove particularly potent in biology and that have been given short shrift in the molecular biology era are strictly phenomenological models that make no reference to underlying “mechanism.” These kinds of laws have formed a centerpiece of physics for more than three hundred years in contexts ranging from the laws of elasticity to hydrodynamics. Here, what I have in mind is a phenomenological link in mathematical terms that connects the variables that have emerged from measurements. Both the familiar Hooke’s law and ideal gas law originally emerged as highly powerful, yet strictly phenomenological reflections of what had been measured in the laboratory. Examples have already started to emerge in physical biology as well. Recent high-resolution measurements make it possible to explore the growth of bacteria resulting in a number of propositions for bacterial growth laws (Harris and Theriot, 2018; Iyer-Biswas et al., 2014; Jun et al., 2018). With no reference to the molecular underpinnings, these phenomenological laws engender corresponding phenomenological hypotheses for how populations of bacterial cells maintain a narrow distribution of cell sizes, such as adder and timer models in which the growing cell either waits to divide until it has added a certain fixed quantity of material or until a fixed amount of time has elapsed (Camos et al., 2014). Another provocative and beautiful set of phenomenological laws has emerged concerning the character of the entire proteome (Schaechter et al.,

1958; Scott et al., 2010). Here, the idea is that the growth rate of cells serves as a kind of “state variable” and that depending upon this growth rate, the fraction of the proteome devoted to protein production (i.e., ribosomes) takes a very specific value. Schrödinger’s chapter 6 asks us to think about the emergence of order from order as seen in Figure 4, a topic that has become central to modern physical biology, whether in the context of bird flocks (Cavagna and Giardina, 2014; Toner and Tu, 1998) or cytoskeleton-motor systems such as those that partition chromosomes during cell division (Marchetti et al., 2013; Needleman and Dogic, 2017; Prost et al., 2015; Ramaswamy, 2010). In all of these cases, phenomenological laws have emerged, and we are now in a stage of science when the laws are tested and refined, the implications are further examined, and efforts are set forth to try and derive those laws from some deeper understanding of the underlying processes.

Some of the many other areas in which I suspect we will find “new physics” focus on the ways in which biological systems locally defy the tendency toward equilibrium. Examples include a series of problems such as the accuracy problem (how biological systems achieve such high fidelity in comparison with what is implied by the “statistical structure” of classical physics), the adaptation problem (how biological systems change their physicochemical behavior in real time in response to environmental cues), the reproducibility problem (how living organisms achieve the same outcome such as the human body plan over and over again in a nearly error-free fashion), and the structure problem (how structures such as the outer segment of photoreceptors are constructed and maintained in the face of the noisy world that surrounds them). I also suspect that there are surprises before us in the unfinished business of dynamics, a subject that started with the great successes of classical mechanics, then to the incomplete promise of thermodynamics, and now the full-fledged challenge of the out-of-equilibrium aspects of biological dynamics, whether the separation of chromosomes or the origin of species. Of course, these “problems” are offered tentatively and subjectively because every generation has to decide what its most pressing problems are, but

my main point is about the kind of solutions that we should demand in accounting for biological phenomena.

A manifesto: Schrödinger’s unfinished business

A perennial question for any scientist is: what to work on? Of course, there is no one right answer and one of my own favorite answers is: whether young or old, scientists should work on whatever they are truly most curious about understanding from the vast array of mysteries presented by the world around us. In academia, much debate and angst are powered by this question in disguise as we ask ourselves, should this person be hired or that grant be funded? One of the ways that people try to sharpen that question is by asking whether we will find new physics or new biology, depending upon within which department that question is considered. For a very thoughtful modern reflection on the question of new physics more broadly by a noted physicist who worked in many domains of physics, see “Does Astronomy Need ‘New Physics?’” (Ginzburg, 2001). Stated most succinctly, Schrödinger’s short work ventures the guess that indeed, by looking at living matter, those who subscribe to the definition of understanding demanded in physics will find new physics there.

As already alluded to throughout the article, the last 30 years have seen enormous progress at the interface between physics and biology. As for whether or not there is new physics to report, I think it depends on how we take that question. If we are practicing what Thomas Kuhn referred to as “normal science,” there is no doubt that there has been an impressive array of results that surely count as new physics. Examples abound, whether in the context of cellular motility, detection, and adaptation in the context of chemotaxis (Berg and Purcell, 1977; Purcell, 1977; Sourjik and Berg, 2002), in the analysis of population genetics with its beautiful analogies between the Boltzmann distribution of statistical mechanics and the distribution of allele frequencies (Lässig 2007), or in the surprising new features revealed in the study of active matter (Toner, 2018). In an excellent series of lectures, John Toner notes: “...the biggest surprise in the entire field of active matter is that a ‘polar ordered dry active

fluid phase' is even possible in two dimensions" (Toner, 2018), technical words behind a fun and interesting example of the new physics that has emerged in thinking about bird flocks. Yet another example is offered by the phenomenon of cytoplasmic streaming (Corti 1774), observed before the founding of the United States, and yet only in the last decade has the natural language of dimensionless variables allowed us to compare the relative importance of diffusion and flow in transporting materials within large cells and to compute the kinds of flow patterns that emerge (Goldstein et al., 2008; Goldstein and van de Meent, 2015; Mayer et al., 2010; Münster et al., 2019). All of these examples constitute the activities of normal science and the act of "doing physics" on them has resulted in not only sharpening our questions, but also in increasing the depth of our understanding. In a playful turn of the millennium piece entitled "Molecular Vitalism," Kirschner, Gerhart, and Mitchison show how many of the issues raised by Schrödinger about what gives living organisms their distinct physicochemical attributes remain as fresh now as they were in the 1940s. "We do not question the importance of genetics, nor dispute the role of DNA as the blueprint for all the components of living systems, but we think it worth asking to what extent the postgenomic view of modern biology would convince a nineteenth century vitalist that the nature of life was now understood" (Kirschner et al., 2000).

If we adopt a more sweeping view in which we ask for a revolution in physics that has come on the heels of investigating biological phenomena, we may need to exercise a little more patience. We shouldn't be surprised by the glacial pace at which we get our revolutions. There was a century between the initial discovery of spectral lines and properly "accounting for" them in the series of classic papers by Schrödinger (Schrödinger 1978). That said, I am wary of the common attitude that, because something has not been done, or worse yet, because a given commentator themselves has not done it, that means that it cannot be done. I suspect that in the physics pedagogy a hundred years hence (if humans are still teaching each other important ideas by then), there will be courses whose central ambition will be to explain

the harvest of the revolution that resulted from physicists trying to answer the question "what is life?" to their own satisfaction, in much the same way that we have physics courses dedicated to the question of "what is matter?"

Despite both the insight and promise of Schrödinger's thinking in *What Is Life?*, not all responses to his book were positive (Dronamraju, 1999). Three greatly accomplished scientists who came down on the negative side of the ledger were famed American geneticist HJ Muller, Caltech chemist and visionary Linus Pauling, and the structural biologist Max Perutz, Schrödinger's compatriot. Their reactions strike to the very heart of how different fields view what questions are interesting and what constitutes acceptable answers to those questions (Keller, 2002). Indeed, as is now clear, a major thrust of this essay has been that in adopting Schrödinger's physicist definition of understanding, we will see that the study of living matter will demand new physics. Though differences in philosophy about what it means to understand something explain some of the negative reaction to Schrödinger's classic, I find a marked lack of generosity given the circumstances of the book's origin as a written summary of public lectures.

In a centenary volume celebrating Schrödinger's contributions to modern science (Kilmister, 1989), Pauling wrote "Schrödinger's discussion of thermodynamics is vague and superficial to an extent that should not be tolerated even in a popular lecture." Writing in the same volume, Perutz is even more scathing, making comments such as, "Sadly, however, 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 the book was written...the apparent contradiction between life and the statistical laws of physics can be resolved by invoking a science largely ignored by Schrödinger. That science is chemistry." Hence, as did Crick, Perutz takes Schrödinger to task for ignoring "chemistry," which he argues would make the stability of genetic information clear. Here, I part ways with Perutz because as our ability to routinely melt DNA in our PCR machines shows, the stability of the genetic material is intimately

related to precisely the thermal physics discussed by Schrödinger. Understanding the high-fidelity of the processes of the central dogma, to name but one example that falls outside the purview of both classical statistical physics and the chemistry of the mid 20th century, demands much more of us than Boltzmann distributions and chemical bonding.

It is intriguing to explore the claim that if Schrödinger had but only appealed to the science of chemistry, no mysteries would have remained for the classical physicist trying to "account for" the living organism. Having spent now nearly a decade trying to come to terms with the field that Perutz was central in creating, namely, the subject of allostery, I remain more skeptical than ever of what I will call the salt-bridge argument (Bettati et al., 1998; Perutz, 1978), an example of the conviction that if we only understand the atomic-level structures of the macromolecules of the living world, then "mechanism" and understanding will unfold before our eyes. Really, what we are talking about here is precisely the kind of polarizing debate that separates our political lives, what Thomas Sowell christened a "conflict of visions." Schrödinger was not invalidating or critiquing the world view of chemists or biologists, he was trying to explain what it looks like for physicists to "account for" a subject. His views are echoed forcefully and eloquently by today's leading biophysical thinkers (Bialek, 2012; Bialek, 2017; Goldstein, 2018; Nelson et al., 2015). The point of my loving review of Schrödinger's little book *What Is Life? 75 years on* is that, to really understand the book's meaning, we have to remember both the question being considered and the audience being addressed. In my view, it is a mistake to think of his work as a manifesto about biology for biologists. It is a manifesto about the frontiers of physics and the way that every time physics tackles new classes of phenomena, it requires new concepts and ultimately results in the formulation of new laws. It is also a manifesto about the unity of nature. Nature cares not for the names of our subjects. Names such as physics and biology are a strictly human conceit, and the understanding of the phenomenon of life might require us to blur the boundaries between these fields.

Sidney Brenner once quipped that, in research, one should either be 6 months ahead of the scientific pack or 30 years behind. There is much to that remark since over and over again, pathbreaking discoveries are made when new technologies are used to reconsider “old” problems. Nowhere is this more true than in the case of the hydrogen atom, one of the most remarkable gifts ever given to science (Rigden, 2002). Hydrogen has served as the quintessential test case for what it means to “account for” the behavior of atoms (spectral lines), the nucleus (the deuteron), the coupling between radiation and matter, Bose-Einstein condensates, and beyond. Similar case studies are only waiting to be exploited in biology once Schrödinger’s notion of what it means to account for a phenomenon is accepted. The study of living matter needs its hydrogen atoms. Erwin Schrödinger’s remarkable *What Is Life?* makes it clear that Brenner could have gone even farther and exhorted us to search 75 years into the past to find an inspiring charge for the future.

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