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Guest editorial

Seeing with an extra sense

Rob Phillips

I am the Lorax! I speak for the trees.
— Dr. Seuss

Science foremost derives from our curiosity about the world. Can we make sense of the phenomena we see around us? Given that understanding, can we predict previously unimagined phenomena? How do things work? Can we use what we discover to invent new technologies? One class of questions that has mesmerized observers, dating at least to early cave paintings of hunters and their prey, surrounds the nature of the phenomenon we refer to as life. Over the centuries, scientists have found a broad array of surprisingly different techniques for observing, measuring, characterizing and explaining the living world. Microscopes provide a dazzling view of a previously unseen reality that tells us how living organisms are made up and how their components are organized and move. The tools of molecular science tell us the sequence and structure of the macromolecules that fill cells. The data explosion that has attended the development of a new generation of high-throughput tools for querying the living world demands that we have some way of accounting for those data that both provide intuition and make dangerous predictions with no after-the-fact parametric wiggle room. In this special issue of *Current Biology*, leading researchers explore how physical approaches have contributed to various fields of biology. Here, to introduce this special issue, I consider some of the ways in which viewing the living through a physical lens allows us to see things that might otherwise remain hidden.

Organizing nature

Many parts of physics explore the remote and unseen, whether the dizzying enormity of the universe first revealed by Galileo's telescope[1] or the tiniest particles whose properties are measured at giant particle accelerators[2]. But there is another part of the natural world that is not remote at all, a world celebrated in nature books and documentaries. Examples include the work of Bernhard and Michael Grzimek or Anthony Sinclair in their accounts of life on the Serengeti[3,4], the undersea world of Jacques Cousteau and others[5], and the adventures of David Attenborough[6], who has brought us pictures and stories of the natural world from all points of the compass. These works come on the heels of the dangerous worldwide explorations of the early naturalists, who made it clear that the study of the natural world right before our eyes can be a scientific study[7]. An inspiring and surprising biography of the great naturalist Alexander von Humboldt is provocatively entitled *The Invention of Nature*[8], making clear that it was an act of creative intelligence to realize that the phenomena of the living world around us as well as its terrestrial substrate are a subject worthy of study as a scientific discipline. As a reminder of Humboldt's instinct for the linkage of living organisms and our planet, readers are invited to examine Humboldt's famed map of the Chimborazo volcano in Ecuador that shows the distribution of species as a function of altitude on the volcano[9]. The work of Humboldt hinted that there might be general principles that would preside over the part of the world that we see when wandering through a forest or trekking up a mountainside or sailing across the wide seas. Long before Dr. Seuss' classic 'children's book' *The Lorax*, Humboldt spoke for the trees. In his essay *Humboldt*, Robert G. Ingersoll noted of Humboldt's view on man and the study of the nature that presents itself right before our eyes, "He came to the conclusion that the source of man's unhappiness is his ignorance of nature." The study of life in the subject of biology allows us to formally revel in the wonders of nature.

Attendant with the study of nature writ large, natural philosophy introduced the twin pillars of, firstly, experimentation and measurement and, secondly, mathematical theorizing to describe phenomena as diverse as the motions of planets (see the masterpiece by Richard Westfall on Newton to get a flavor for the rise

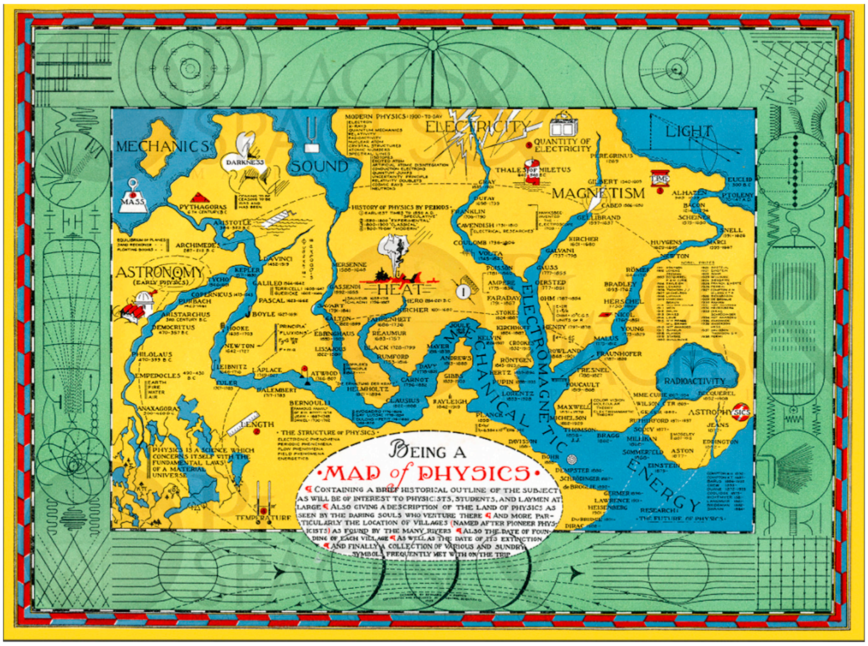
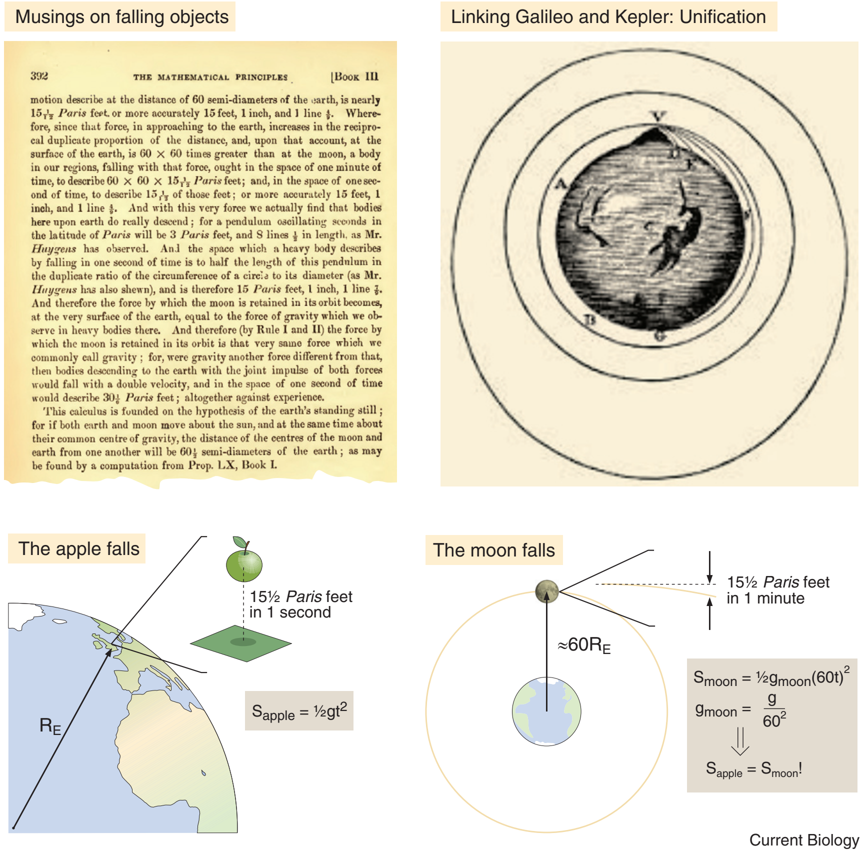


Figure 1. Porter's *Map of Physics*.
Off the map is another continent, that of biology. Many of the insights learned to navigate the world of condensed matter physics by Philip Anderson and others as explained in his 1972 essay 'More is different' can be used when marauding over the seemingly completely different contours of the biological continent[91,116]. Further, some of these insights from physics can serve as a bridge between those two continents. (Reprinted by permission of Mark Melnicove, literary executor, The Bern Porter Estate, mmelnicove@gmail.com.)

of natural philosophy at its best[10]) or the stoichiometric equation for photosynthesis (see the brilliant description of the "pneumochemists" and their measurements of the reactants and products of photosynthesis in chapter 1 of the book by Rabinowitch and Govindjee[11]). However, with its growing intellectual maturity, natural philosophy slowly splintered into separate subjects of enquiry, with physics serving as an especially potent example, itself divided into subjects now canonized as mechanics, electricity and magnetism, thermodynamics and statistical mechanics, quantum mechanics and relativity (see[12,13] for several very creative examples of the partitioning of the entire subject of physics). In the 1940s, Porter provided a map of what he thought of as the great continent of physics as shown in Figure 1.

Although it is a superficial rendering of the history of physics, I note here that, over and over again, digging quantitatively and deeply into the phenomena of the natural world inevitably leads to 'new physics'. If we think of the phenomena of the natural world as a vast continent, since Newton's 1687 path-breaking *Principia Mathematica*[10,14], different parts of that continent have been explored at higher resolution[15,16]. As seen in Figure 1, as of the 1940s, the continent of physics looks to the modern eyes much like the 1507 map of the world known as the Waldseemüller map or *Universalis Cosmographia*. Obviously, the map bears many resemblances to our modern understanding of physics in much the same way that the Waldseemüller map gives a distorted image of the Mediterranean region. On the other hand, vast parts of the continent of physics are missing and the map doesn't even acknowledge the existence of other continents. The subject of this editorial is how our explorations of the continent of physics have taught us key lessons for investigating the vast continent of biology and where to find the land bridges that now connect it to the continent of physics.

There is a part of the universe that we call living. Clearly, there are many ways to organize our understanding of that part of nature[17], whether through the powerful tools of molecular biology[18,19], the razor sharp logic of genetics[20,21], the beautiful microscopic dissections of cell biology[22–24], the mechanistic and *in vitro* reconstitutions of biochemistry[25,26], or the sweeping vision of evolution[27–31]. Here, I discuss another key approach — namely, the physical dissection of the phenomena of life[32–35].


Musings on falling objects

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motion describe at the distance of 60 semi-diameters of the earth, is nearly $15\frac{1}{12}$ *Paris* feet, or more accurately 15 feet, 1 inch, and 1 line $\frac{4}{9}$. Wherefore, since that force, in approaching to the earth, increases in the reciprocal duplicate proportion of the distance, and, upon that account, at the surface of the earth, is 60 × 60 times greater than at the moon, a body in our regions, falling with that force, ought in the space of one minute of time, to describe $60 \times 60 \times 15\frac{1}{12}$ *Paris* feet; and, in the space of one second of time, to describe $15\frac{1}{12}$ of those feet; or more accurately 15 feet, 1 inch, and 1 line $\frac{4}{9}$. And with this very force we actually find that bodies here upon earth do really descend; for a pendulum oscillating seconds in the latitude of *Paris* will be 3 *Paris* feet, and 8 lines $\frac{1}{2}$ in length, as Mr. *Huygens* has observed. And the space which a heavy body describes by falling in one second of time is to half the length of this pendulum in the duplicate ratio of the circumference of a circle to its diameter (as Mr. *Huygens* has also shewn), and is therefore 15 *Paris* feet, 1 inch, 1 line $\frac{7}{9}$. And therefore the force by which the moon is retained in its orbit becomes, at the very surface of the earth, equal to the force of gravity which we observe in heavy bodies there. And therefore (by Rule I and II) the force by which the moon is retained in its orbit is that very same force which we commonly call gravity; for, were gravity another force different from that, then bodies descending to the earth with the joint impulse of both forces would fall with a double velocity, and in the space of one second of time would describe $30\frac{1}{6}$ *Paris* feet; altogether against experience.

This calculus is founded on the hypothesis of the earth's standing still; for if both earth and moon move about the sun, and at the same time about their common centre of gravity, the distance of the centres of the moon and earth from one another will be $60\frac{1}{2}$ semi-diameters of the earth; as may be found by a computation from Prop. LX, Book I.

Linking Galileo and Kepler: Unification

The apple falls

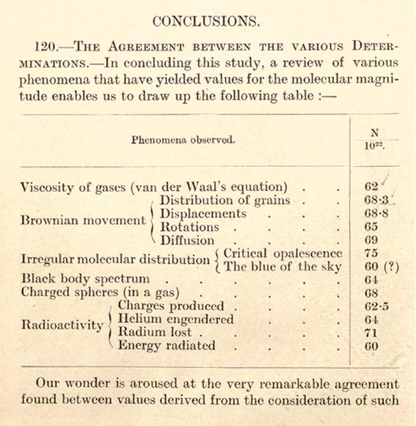
The moon falls

Current Biology

Figure 2. Newton's unification of terrestrial and celestial motion.
A page taken from Newton's masterpiece, the *Principia Mathematica*, shows him comparing the distance fallen by an object on the Earth and the distance 'fallen' by the moon. The essence of that calculation is schematized in the two panels at the bottom of the figure. The figure in the upper right is Newton's recognition that the parabolic trajectories of Galileo and the elliptical orbits of Kepler can be unified when viewed through the unifying power of the law of universal gravitation.

The hallmarks of a physical dissection

What are the hallmarks of the physical dissection of a natural phenomenon? To answer that question, the argument I will make here is that physics can be viewed as a style rather than a subject. That style is revealed in many different ways, most of which I suspect can be powerful tools in the study of life. Perhaps the most attractive feature of physical dissections is the way in which general principles can explain broad swathes of apparently unrelated phenomena (though it should be known that eminent biologists such as Ernst Mayr concluded that biology is an autonomous science which does not permit such principles[17]). A beautiful, famous and inspiring historical example of the unifying power of such principles is shown in Figure 2, where we see how the apparently distinct phenomena of Galileo's projectile motion and Kepler's elliptical orbits are both manifestations of Newton's second law of motion in conjunction with the law of universal gravitation. The Newton example already features many of the key hallmarks of a physical dissection: the unexpected unification of distinct phenomena, theoretical approaches based on the pillars of abstraction, simplification and idealization (for example, Newton's initial approximation of the Earth as a point mass), and the use of theoretical principles to make predictions about a wide variety of phenomena (tides, the



CONCLUSIONS.

120.—The Agreement between the various Determinations.—In concluding this study, a review of various phenomena that have yielded values for the molecular magnitude enables us to draw up the following table :—

Phenomena observed.		$\frac{N}{10^{22}}$.
Viscosity of gases (van der Waal's equation)		62
Brownian movement	Distribution of grains	68·3
	Displacements	68·8
	Rotations	65
	Diffusion	69
Irregular molecular distribution	Critical opalescence	75
	The blue of the sky	60 (?)
Black body spectrum		64
Charged spheres (in a gas)		68
Radioactivity	Charges produced	62·5
	Helium engendered	64
	Radium lost	71
	Energy radiated	60

Our wonder is aroused at the very remarkable agreement found between values derived from the consideration of such

Figure 3. Multiple ways of measuring Avogadro's number.
Reused from Jean Perrin, *Atoms*[117].

shape of the earth, the orbits of comets, etc.). Often, our physical theories can be thought of as *effective theories* that do not feature all of the degrees of freedom, whether in the Superb Theorems of Newton in which he showed that two spherical masses could be thought of as point masses[14] or the theories of mass (Fick's law) and heat (Fourier's law) diffusion which make no reference to the underlying molecular reality. This emphasis on simplification goes even further through a fundamental belief in the instructive value of 'toy models', because often such toy models help us understand not only what is, but also what is possible. Both Carnot and Shannon provided deep insights into what is possible with heat engines and information transmission.

An allied facet of the physics style is a great emphasis on the careful design of experiments that aim to precisely measure some quantity of underlying theoretical interest. This philosophy is perhaps best embodied in the approach of Michael Faraday, arguably one of the greatest experimental scientists in history and about whom John Tyndall remarked: "His principal researches are all connected by an undercurrent of speculation. Theoretic ideas were the very sap of his intellect — the source from which all his strength as an experimenter was derived. And so it must always be: the great experimentalist must ever be the habitual theorist, whether or not he gives to his theories formal enunciation."[36]. Figure 3 gives an example of the idea of precision measurement in the all-important example of Avogadro's number, illustrating as much a focus on rigor as on 'novelty'. See the fascinating article of Pauling in which he describes how Avogadro began to solve the problem of "finding out how many atoms of different kinds are involved in the molecules or crystals of the substances"[37]. Though I have used the example of the determination of Avogadro's number elsewhere[38], the fundamental message is timeless and worth repeating. This example shows the absolute *requirement* that our understanding of different phenomena be coherent, as evidenced by the so many distinct and surprisingly different ways of measuring the atomic magnitude. A lack of such coherence and internal self-consistency characterized the 19th century debate on the age of the Earth[39] and the sun[40], with Lord Kelvin tormenting Charles Darwin so much that Darwin wrote in a letter to Alfred Russel Wallace that Kelvin's "views on the recent age of the world have been for some time one of my sorest troubles". The physical mindset demanded a relentless pursuit of a detailed, coherent explanation of the ages of the Earth, the sun, the fossils on Earth, the energy source of the sun, and so on[41], such that now the biology, the geology, the physics and the astrophysics are all largely internally consistent.

I make no claim that the approach of carrying out a physical dissection is the only or even the best way to tackle the subject of the living. What I argue instead is that this approach is insightful, beautiful and fun.

The living through the physical biology lens

One of the ways that I will organize my thinking about the role of physics in the study of the living is through a series of propositions. Each proposition provides an assertion for the reader's consideration as a way in which a physical mindset might reveal new and potent ways of thinking about the many phenomena of life. Below I offer eight such propositions.

Expanding our umwelt

The study of the natural world can leave all of us with a sense of humility. There is so much we don't know. In the biological context, this idea has been crystallized through the notion of *umwelt*, a noun that stands for the *perceived* environment[42]. No example that clarifies the meaning of umwelt means more to me than the lifestyles of cetaceans. These are the beautiful and enigmatic marine mammals such as the dolphins that play in the bow wakes of boats or the sperm whales that dive to the silent darkness a kilometer beneath the surface of the ocean in search of giant squid[43,44]. The reason I find the cetacean example as a most compelling case study in umwelt is because of the ways in which these animals navigate a world that is for us at once dark and silent and yet to them is teeming with activity. To get a feeling for the limitations of our own umwelt and the ways in which cetaceans perceive a world that is unseen to us, Figure 4 shows an experiment carried out with trained dolphins in which they are asked to distinguish between two nearly identical metal cylinders from a distance of nearly 10 meters[45,46]. The two hollow cylinders differ only in the fact that their inner diameters are slightly different. As seen in the figure, using their echolocation technologies, the dolphins can, with nearly 100% accuracy, tell the difference between the cylinders as long as the inner diameters differ by more than 0.5 millimeters. Imagine!

What does all of this have to do with the ways in which a physical or mathematical mindset might yield new insights into the nature of life? Well, perhaps the obvious answer is that it takes physical approaches to dissect the various kinds of umwelt exploited by animals as they migrate and hunt, in much the same way that brilliant work has probed the limits of human vision, hearing and olfaction, for example[47]. But my deeper metaphorical point is that there are many ways to perceive natural phenomena and that, through the use of a physico-mathematical mindset, we can expand our umwelt, literally seeing things about biological phenomena that are otherwise invisible[35,48].In his *Autobiography*, written for his family members, Charles Darwin made this point vividly in a way that gave rise to the title of this editorial: "I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics, for those thus endowed seem to have an extra sense."[49]. The physico-mathematical mindset expands our umwelt by providing an extra sense with which to gaze upon the wonders of the living world around us.

"What sets the scale of X?" thinking

One of the ways in which the physical mindset expands the umwelt of any subject it touches is through an emphasis on the all-important question of "What sets the scale of X?". I would go so far as to say that if we are not able to answer that question about a given phenomenon, then we don't understand it. A few examples of "what sets the scale of X?" questions that I hope will fire the imaginations of my readers inspiring them to take up pencil in hand are: What sets the scale of the power per kilogram of a person and how does that compare to the power per kilogram of the sun? What sets the scale of the fraction of sites on a protein that are phosphorylated? What sets the scale of the time for one ribosome to make another? What sets the timescale for a cell to exhaust all of its ATP if the machinery of ATP synthesis is shut down? How much poop was lost in the oceans in the 20th century due to the killing of roughly 3 million whales and how does that poop compare to the total fertilizer use on the planet? What sets the error rate of DNA copying and how does it compare to the error rate in Amazon's Kindle books? What sets the scale of the volume of water taken up by a baleen whale per lunge? What sets the scale of the time of a whale's dive and how many lunges per dive and per day? What sets the scale of the minimum number of odorant molecules that can be detected? and on and on. What sets the scale of X? Evelyn Fox Keller's excellent biography[50] of Barbara McClintock noted that McClintock argued that, above all, one must have "a feeling for the organism", and my argument is that the insistence on answering "What sets the scale of X?" questions is the way in which the physical mindset delivers a feeling for the organism.

Accounting for the living

Different people and different fields have different ideas about what it means to understand something. The physical mindset offers one such perspective on what it means to understand a biological phenomenon. In a series of popular lectures in the early 1940s, Erwin Schrödinger explored the question of what it might look like to a biology-loving physicist to tackle the nature of the living[51,52]. 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?" One of the most important offerings of viewing life through the physical biology lens all centers on the words "account for". When Schrödinger used the words to "account for", my interpretation is that he was harkening back to the example of his own work on a full explanation of the behavior of electrons in contexts such as atoms and molecules[53]. In particular, he was able to nearly completely "account for" the measured spectral lines of hydrogen. Very specifically, the empirical formula of Balmer reports the wavelengths of the spectral lines of hydrogen as:

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

where λ is the wavelength of the spectral line in question, R is a phenomenological parameter known as the Rydberg constant, and p and n are integers. But in Schrödinger's hands, this formula became a result. Using the wave equation that now bears his name, Schrödinger derived a formula for the energy levels of the hydrogen atom that made it possible to compute the wavelengths of the spectral lines of hydrogen with no phenomenological parameters. Now instead of being an empirical parameter, the Rydberg constant could be understood from first principles as:

$$R = \frac{me^4}{8h^3 c\varepsilon_0^2} \approx 1.1 \times 10^7 m^{-1}$$

(Equation 2)

featuring fundamental constants of physics, such as the mass of the electron m, the charge on the electron e, the speed of light c and Planck's constant h. This is what it means to "account for" a class of phenomena.

Indeed, the power with which quantum mechanics revealed the secrets of the hydrogen atom led to the habit of calling a given problem that has the power to teach general principles through its specificity the 'hydrogen atom' of a given subject. This name refers to the way that deep immersion in the study of the properties of hydrogen ended up teaching us the general principles for the entirety of the microscopic world[54]. The point is that, by digging deeply into a specific problem, demanding

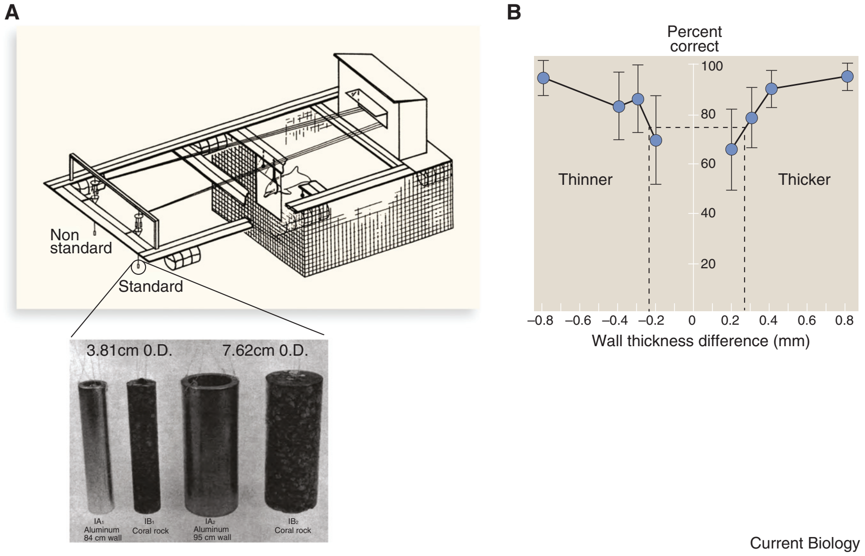


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Figure 4. The umwelt of the dolphin.

(A) The schematic illustrates how a dolphin is immobilized for the purposes of distinguishing the standard and non-standard cylinders. (B) The accuracy with which the dolphin can distinguish the two cylinders as a function of the difference in the wall thicknesses. (Used with permission from Springer Nature BV, from Au[45].)

the complete and rigorous success of the theory–experiment dialogue yields unexpected dividends in the study of apparently unrelated problems. Sometimes, there is a perception that by digging down into something ‘we already know’ we are doing nothing more than ‘dotting ‘i’s’ and crossing ‘t’s’ ’, but my argument here is that this is quite misguided. As usual, I think the history of science has much to teach us and what we will see is that digging deeper into specific, detailed case studies yields massive general insights.

In fact, there are already a suite of powerful examples of ‘hydrogen atoms’ in the study of life as well. One of the most familiar examples is the role played by the *lac* operon in the quantitative study of gene expression[55–58]. Indeed, the quantitative dissection of this system has become so sophisticated that curves comparing parameter-free predictions and measurements could pass as results from condensed matter physics if the labels on the axes were changed from biological variables, such as level of gene expression (output) and transcription factor copy number (input), to variables describing a physical input–output function, such as current (output) and voltage (input)[59–61]. Perhaps an even more impressive example of a biological ‘hydrogen atom’ is offered by the study of bacterial chemotaxis. As with the example described above, the comparison between theory and experiment, even for a suite of different mutants, leads to the ability to collapse all of the data on one master input–output curve[62–65].

As a precise fascinating current biological example of an emerging ‘hydrogen atom’ in the study of the dynamics of living organisms, we consider the mysterious and beautiful phenomenon of regeneration. In the mid-1700s, a Swiss biologist by the name of Abraham Trembley had come to the Netherlands to tutor the children of Count William Bentinck at their summer estate, Sorghvliet. Little did he know that the tiny creatures he would find in the ponds and canals would revolutionize biology. What Trembley did was in modern parlance to establish a powerful new model organism, now known simply as *Hydra*. Through careful experimentation, Trembley realized that tiny pieces of the animal could be excised and that these fragments over a period of several days would transform into a complete animal, apparently indistinguishable from its butchered ancestor.

What I find so especially beautiful about this surprising study is the way it teaches us that nature doesn’t care about our artificial disciplinary boundaries, celebrated by giant buildings and centers with fancy titles[66,67]. In this case, a most biological of examples, the regeneration of microscopic organisms from pond water leads us to the molecular biology of cytoskeletal filaments and from there to the topological defects seen in our fingerprints[68]. Using the modern tools of cell biology and condensed matter physics, it is now possible to watch the regeneration process in real time while keeping track of the local ordering of actin filaments.

In the biological context, Schrödinger’s notion of “accounting for” lays down a challenge across different spatial, temporal and energy scales. There are a host of questions where there is now the promise of this kind of accounting, whether in computing the phase diagrams for condensates in living cells[69] or the mechanisms of size control of flagella[70] or the level of expression of different genes as a function of inducer concentration[60]. My main point is that the physical mindset offers a different and potent view of what it means to account for the phenomena of the living and suggests that, when we achieve that kind of understanding in a particular problem, it can be canonized as the ‘hydrogen atom’ of our subject.

Seeing the sameness in difference

For me, one of the most surprising outcomes of learning a little physics was the profound insight that phenomena that are ostensibly quite distinct can in fact be quite literally the same. A most important example of the sameness of phenomena is offered by simple harmonic motion, the rhythmic dynamics first carefully examined by Galileo in the swinging of a cathedral chandelier and celebrated in modern form in the equation:

$$m\frac{d^2x}{dt^2} + \gamma\frac{dx}{dt} + kx = F(t)$$

(Equation 3)

where $x(t)$ is the position of the mass m, γ is the drag coefficient, k is the spring constant and $F(t)$ is the external load on the mass. In this case, the dynamical equation arises from following the paradigm of the mechanical world view in which we use Newton’s second law of motion $F = ma$ to find the position of a particle as a function of time, what we are calling $x(t)$. The surprising sameness appears when we investigate the motion of charge (better known as current, $i = dq/dt$) in a circuit involving resistors, capacitors and inductors, resulting in a dynamical equation for the charge $q(t)$ as a function of time and given by:

$$L\frac{d^2q}{dt^2} + R\frac{dq}{dt} + Cq = V(t)$$

(Equation 4)

where the inductance L plays the role of mass, the resistance R is analogous to the damping, the capacitance C behaves like a spring constant and $V(t)$ is the applied voltage. The mathematical structure of these two equations is literally identical, which means that our understanding of the one is serviced by our understanding of the other (this point is made beautifully in the great book by Anthony French[71]).

An even more impressive example of this sameness comes in the form of the many uses to which the diffusion equation can be put in the service of biology. This conceptual framework can be used to explore everything from the motion of fluorophores to the conformational structure of polymers such as DNA to the phenomenon of genetic drift, whereby evolution occurs not because of selection but instead because of diffusion in allele frequency space[72]. However, my personal favorite of biological sameness is offered by the all-important phenomenon of allostery[73–77], once referred to by one of the subject’s founders, Jacques Monod, as “the second secret of life”[78]. The allostery concept refers to the fact that many of the macromolecules of life, with special reference to proteins, can exist in two (or more) states of activity, one that is competent to perform some task, such as carry out an enzymatic reaction or activate transcription, and a second state that cannot perform this task. The balance between these two states is driven by the binding of some ‘effector’ molecule. The sameness of these different examples, ranging from ion channels to hemoglobin to transcription factors to enzymes, is captured in the form of the statistical mechanical model used to compute the probabilities of these different states, which carries the specific details of a given molecular system only in the form of one of three or four underlying parameters. All of these seemingly disparate examples (e.g., ion channels, transcription factors, enzymes, membrane receptors, etc.) are to a first approximation described by the same fundamental equation (the one equation that rules them all) that serves as the central equation of allostery, namely:

$$p_{active}(c) = \frac{\left(1+\frac{c}{K_A}\right)^n}{\left(1+\frac{c}{K_A}\right)^n + e^{-\beta\varepsilon}\left(1+\frac{c}{K_I}\right)^n}.$$

(Equation 5)

This equation tells us the probability of a molecule with *n* binding sites for ligands being in its active state as a function of ligand concentration *c* in terms of the energy difference between the inactive and active conformations ε, and the dissociation constants K_A and K_I of these ligands for the active and inactive states, respectively. One of the most brilliant examples of the possible sameness between different phenomena was the suggestion of an analogy between nucleosome remodeling and the Bohr effect in hemoglobin[79]. Like the best models, this one suggested further experiments that led to the conclusion that the model remains incomplete[80].

Sharpening our null hypothesis

Though we don't talk about it this way, science is built up of cycles of guesswork, where we make these guesses sound more sophisticated than they are by disguising them with the word hypothesis. One of the most important propositions that I am making about the physics mindset is that it forces us to sharpen our hypotheses by making them quantitative. Reflections on the history of physics make it clear how often our leading hypotheses are wrong. In the early 19th century, it was thought that heat was a fluid named caloric, a hypothesis that was part of the thinking of Sadi Carnot in his quite successful attempt to understand the general rules setting the efficiency of heat engines[81]. Maxwell imagined vortices in the ether, a hypothetical medium that was part of the intellectual landscape for nearly the entire 19th century[15,16]. An especially compelling description of the many 'wrong' hypotheses that have colored the history of physics is offered by the book of Longair[16]. In an article that I think should be mandatory reading for all students of biology, Jeremy Gunawardena introduces us to the notion of "pathetic thinking" described by Sir James Black in the context of formulating mathematical statements of our hypotheses[35,48]. Black had noted: "Models in analytical pharmacology are not meant to be descriptions, pathetic descriptions, of nature; they are designed to be accurate descriptions of our pathetic thinking about nature." In my view, it is a total illusion for any scientist[82], no matter what their background, to think that their hypothesis-making is somehow insulated from the risk of being wrong. Or even more importantly, some espouse the conviction that by framing our hypotheses in mathematical language, they are *more* likely to be wrong[83]. The physico-mathematical mindset discussed here and celebrated by Black and Gunawardena and by Goldstein as well[35,48] helps us see our way more quickly to the flaws in our hypothesis-making. To be clear, let's consider several examples.

The study of genes and how they are deployed in space and time is one of the most important endeavors in modern biology, touching on problems ranging from embryonic development to bacterial persistence in the face of antibiotics. A signature feature of physical approaches to problems in understanding the world around us is a rigorous interplay between theory and experiment. With the advent of tools for measuring gene expression at the single-cell level, this means we can now construct the entire mRNA distribution, the frequency of counts of mRNA at the single-cell level. From a theoretical perspective, there are several possible null models of how gene expression works. The simplest such model is the so-called constitutive promoter in which a given promoter is an mRNA factory, producing mRNA at a rate *r*. In this case, one can show that the steady-state distribution is Poisson[83] with the probability of finding *m* mRNA molecules given by:

$$p(m) = \frac{\left(\frac{r}{\gamma}\right)^m e^{r/\gamma}}{m!}$$

(Equation 6)

where r/γ is the mean number of mRNA molecules per cell given as a ratio of the transcription rate *r* and the degradation rate γ. In some rare instances, the observed mRNA distribution takes the Poisson form, but more often than not it doesn't. For an example, see the beautiful work of Zenklusen *et al.*[84]. As a result, we form a new null hypothesis — the so-called two-state promoter, in which it is assumed that the promoter can exist in two distinct states, an active state that produces mRNA and an inactive state in which it does not[84,85]. This null hypothesis can be scrutinized in turn, and it is found to serve as a more reliable guide for launching into the transcriptional unknown.

A second compelling example of the power of sharpening our null hypotheses is given by the question of cell-size control. Experiments in prokaryotes and eukaryotes alike make clear that the question of how precisely cells control their size upon division is a quantitative one[86–89]. To give a rough impression of the null hypotheses that have been set forth to greet this question, we can classify them using the language of timer models, sizer models and adder models. The essence of these models is that: in the timer model, the cell waits a certain time after cell division before dividing; in the sizer model, the cells wait until they have achieved a certain size before dividing; and in the adder model, the cells add a fixed amount of material before dividing. This is a deep and subtle topic and we don't have room to enter into the niceties and nuance. The main point I want to make here is that one of the outcomes of sharpening our hypotheses mathematically is that these different models have different predictions about how the fluctuations (e.g. the variance in cell size) will scale as a function of the number of generations of division. In the absence of the null hypotheses, we don't know how to begin in the formulation of our quantitative prejudice. Though prejudice in life is often a bad idea, quantitative prejudice in science is indispensable.

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More Is Different

Broken symmetry and the nature of
the hierarchical structure of science.

P. W. Anderson

The reductionist hypothesis may still be a topic for controversy among philosophers, but among the great majority of active scientists I think it is accepted without question. The workings of our minds and bodies, and of all the animate or inanimate matter of which we have any detailed knowledge are as-

planation of phenomena in terms of known fundamental laws. As always, distinctions of this kind are not unambiguous, but they are clear in most cases. Solid state physics, plasma physics, and perhaps also biology are extensive. High energy physics and a good part of nuclear physics are intensive. There is always much less intensive research going on than extensive.

less relevance they seem to have to the very real problems of the rest of science, much less to those of society.

The constructionist hypothesis breaks down when confronted with the twin difficulties of scale and complexity. The behavior of large and complex aggregates of elementary particles, it turns out, is not to be understood in terms of a simple extrapolation of the properties of a few particles. Instead, at each level of complexity entirely new properties appear, and the understanding of the new behaviors requires research which I think is as fundamental in its nature as any other. That is, it seems to me that one may array the sciences roughly linearly in a hierarchy, according to the idea: The elementary entities of science X obey the laws of science Y.

X	Y
solid state or many-body physics	elementary particle physics

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Figure 5. Philip Anderson and his famed 1972 article.
The great material idealizations of elasticity and hydrodynamics point the way to the power of solids and fluids without the molecules, illustrating the enormous intellectual reach of completely different levels of description. Different both because the fundamental 'units' of enquiry are different and because we pass from the discrete to the continuous. Science screenshot used with permission from AAAS, from https://www.jstor.org/stable/1734697?seq=1#metadata_info_tab_contents. Photo of Anderson from[118], reproduced with permission from SNCSC. Steel without iron image © by[119]. Reproduced with permission of Taylor and Francis Group, LLC, a division of Informa plc. Vortices image from[94], re-used with permission from John Wiley and Sons.

The insulation of phenomena: X without Y

To explain the sharp patterns of clouds we see out of an airplane window, we don't need to make any reference to the underlying O_2 and N_2 molecules that constitute the majority of the $\approx 10^{44}$ molecules making up our atmosphere, and, even less so, would anyone consider it prudent to try to connect the forces holding the nuclei of atoms making up those molecules to the hydrodynamics of the atmosphere. This perspective was articulated beautifully by Kenneth Wilson, one of the principal architects of one of the most profound insights of modern physics, the renormalization group: "If it were necessary in the equations of hydrodynamics to specify the motion of every water molecule, a theory of ocean waves would be far beyond the means of 20th-century science."[90]. As seen in Figure 5, we recently passed the 50th anniversary of Philip Anderson's 1972 article 'More is different', one of the most profound reflections on the way in which phenomena at one scale are insulated from those at another scale that I am aware of[91]. Perhaps one way of couching Anderson's argument as it pertained to the physics of the time is to note that understanding the geography of the province of elementary particles may tell us next to nothing about how to navigate on the landscape of the province of solid materials. There were deep arguments within the physics community as to what constitutes 'fundamental' parts of the science of physics, perhaps similar to the dichotomy that sometimes arises in distinguishing pure and applied mathematics[92]. To push the continent of physics analogy probably too far, learning how to read maps at all is a skill that can be brought along with us as we travel from one locale to another[91,93].

However, the argument being made here is that the insights of Anderson for the physics of 1972 are as valid now as they ever were, but in this case with reference to the way we think about biological understanding. The position of the elementary-particle fundamentalists in physics has now been taken up by the molecular-biology fundamentalists. The argument now might go something like this: a 'fundamental' mechanistic understanding of biological phenomena requires us to describe those phenomena in terms of the structure and function of the molecules that make up those phenomena. But clearly this logic must be found wanting at some point[17]. No description of the macromolecules of the cell places any emphasis on quarks, and yet we know that these are the 'fundamental' constituents of the nucleons making up the nuclei making up the atoms making up the molecules[94]! Most scientists would find it laughable to insist on a quark-level description of hemoglobin, but it is not as laughable as it sounds since that same kind of extreme perspective is offered every time someone insists that the 'right' level of description of some biological phenomenon is molecular. Anderson introduces a simple slogan to make his point: "But this hierarchy does not imply that science X is 'just applied Y'. At each stage, entirely new laws, concepts, and generalizations are necessary, requiring inspiration and creativity to just as great a degree as in the previous one." But here I want to go further. In many cases, it is better to describe X without Y, even though we know perfectly well that Y is there. Whether in ignoring the iron atoms in the bridge shown in Figure 5 or in ignoring the molecules of the atmosphere shown in the vortices in the cloud pattern shown in another panel of this figure, often X without Y is the most judicious, enlightening and predictive strategy.

Rather than using a molecular example, let's think instead about how to describe the structure of a herd of wildebeest or a flock of sheep or a flock of birds as shown in Figure 5. In principle, one might be tempted by the idea of a 'microscopic' description featuring the individual animals. This is the 'molecular' interpretation of herding or flocking. A beautiful alternative description in the spirit of X without Y is to use the hydrodynamic theory of Toner and Tu[95,96]. Their theory is to the study of collective animal motion what the Navier-Stokes equations are to the study of fluid mechanics. Just as Navier-Stokes provides a theory of water that is water without H_2O as explained in the quote from Wilson above, Toner–Tu is herds without animals, a coarse graining to be celebrated, not denigrated. Figure 5 offers other examples such as the French flag model of anterior–posterior patterning in embryonic development where there is no reference to the underlying cells[97–99], or the Monod–Wyman–Changeux statistical mechanical model of allosteric molecules in which all molecular details are subsumed into four simple parameters making it a kind of molecular description without molecules[73–77].

Another way of stating the case is by celebrating what are sometimes pejoratively referred to as phenomenological models. ChatGPT does an admirable job of capturing the essence of such models: "A phenomenological model in physics is a type of model that focuses on describing phenomena based on observed behaviors without necessarily delving into the underlying fundamental mechanisms or theories. The main aim of these models is to correlate empirical data and provide a mathematical formulation that can predict outcomes under similar conditions." Examples abound. The ideal gas law and its amendment in the form of the van der Waals equation of state are both extremely powerful phenomenological models[100]. Our descriptions of the response of materials to gradients of various kinds — Hooke's law, Newtonian viscosity, Fourier's Law and others — are all examples of phenomenological constitutive models of material response. More recently, the Landau theory of phase transitions, perhaps with special reference to ideas such as the Ginzburg–Landau theory of superconductivity, illustrates that these approaches are all going strong. In the end, the main point is that we unapologetically embrace phenomenological models as a formal way of doing the science of X without Y. This is a strategy that can greatly strengthen our approach to studying life.

Diversity versus unity

Charles Darwin's *On the Origin of Species* has only one figure, a primitive version of the history of life as a tree with many branches. On page 159 of the 1859 edition of this great book, Darwin says of his conception of the diversity of life: "The green and budding twigs may represent existing species; and those produced during former years may represent the long succession of extinct species… the great Tree of Life… which fills with its dead and broken branches the crust of the earth, and covers the earth with ever-branching and beautiful ramifications." I am 100% sympathetic: the study of the great diversity of living beings, both past and present, is one of the great and beautiful challenges of the study of the living.

But a physical mindset calls out a different aspect of the living: namely, its unity. An example of this unity was offered above in the context of allostery where I argued that the description of receptors such as the nicotinic acetylcholine receptor can be the same as that for hemoglobin or the *lac* repressor. But before getting into the notion of unity in biology, let's briefly revisit the word 'unification' as it applies in physics, since maybe that will clarify what those with a physical mindset have in mind when thinking about the unity of biological phenomena. One of the greatest figures in the history of science is shown in Figure 2, which illustrates how Isaac Newton, in the process of creating one of the deep branches of physics, namely mechanics, unified our understanding of terrestrial dynamics such as the projectile motion of Galileo with celestial mechanics and the elliptical orbits of Kepler. An equally impressive second example from the 19th century was the experimental program of Michael Faraday, who had an intuition that the phenomena of electricity, magnetism and light were all manifestations of some deeper underlying reality. In the 1830s, Faraday's article of faith culminated in his discovery of electromagnetic induction when he learned that, by plunging a magnet through a loop of wire, a transient electric current would be produced. The mathematical expression of this unification is embodied in the famed Maxwell equations, which in turn expressed the speed of light $c = 1/\sqrt{(\varepsilon_0\mu_0)}$ in terms of the electrical (ε_0) and magnetic (μ_0) properties of free space. These examples are offered to illustrate the way in which unexpected conceptual insights teach us that certain phenomena are the manifestation of some specific underlying principle, unifying those phenomena in previously unexpected ways.

There are many kinds of unity in biology. The example of allostery already mentioned several times was characterized by one of its discoverers as the second secret of life[78], and rightly so. Another example that I think has much broader reach than we know thus far is the use of graph theory as the mathematical language to describe all sorts of kinetic processes from signaling to transcription and well beyond[101–103]. In this case, there are general theorems in play that allow us to make unifying statements that are independent of molecular or biological particulars. Another example is the way in which cells have to measure concentrations: the same physical mechanisms underly the measurement of concentrations by bacteria undergoing chemotaxis[62,65] and the cells in the *Drosophila* embryo that are 'measuring' their position along the anterior–posterior axis, for example, by counting Bicoid molecules[99,104]. In both cases, when assessing the change in concentration $\Delta c/c_0$, the question of how long a measurement needs to be made to achieve a certain precision is described by the same underlying formula[105].

Conceptual versus factual knowledge

What does it mean to know? In my view, one of the lessons that the style we call physics places front and center is the difference between factual and conceptual knowledge. Obviously, as noted particularly eloquently long ago by Eddington, "for the truth of the conclusions of physical science, observation is the supreme Court of Appeal"[106]. Without factual knowledge there is no science. And I note in passing that the whole point of a scientific fact is that there is no such thing as ‘alternative facts’: regardless of when and where, careful scientists will agree on the factual content present in the value of Avogadro’s number or the speed of light. But the whole point of the scientific study of the natural world is to provide intellectual frameworks that take that world’s dizzying factual complexity and turn it into cogent and coherent narratives. Many readers will know of Borges classic short, short story *On Exactitude in Science* in which he tells of a land where the mapmakers make maps as big as the empire itself. The story ends by noting that such maps are useless. Conceptual knowledge is the way that we make sure our maps are not the size of the empire itself.

All fields of science have their unifying conceptual knowledge. Physics really got kicked off by the way in which first Kepler and then more dramatically Newton tamed the complexity of the factual knowledge of planetary motion discovered by Brahe[14,107,108]. Similarly, Darwin and Wallace, followed by many others in the context of the modern synthesis, saw evolution as a way to explain the diversity of life on Earth[27–31]. Plate tectonics provided a unifying perspective on the history of the Earth[109,110], which as a conceptual framework makes a coherent narrative around why whale fossils would be found in the Himalayas of Pakistan. However, in this era of ‘big data’ my sense is that the physics mindset can remind us that, in our study of life, quantitative conceptual frameworks are the greatest challenge of the time. What I mean by this is that now more than ever there is an emphasis on data, whereas I suspect that now more than ever there should be an emphasis on ideas, principles, concepts and laws[111,112]. I have heard it said: “If you are not using AI every day, you are not doing your job.” Given my own very intimate relationship with ChatGPT, which this very morning gave me a helpful description of the enamelin gene that is pseudogenized in many mammals[113], I can accept that point of view. On the other hand, this does not mean we can abdicate our instinct for what it means to understand something to the machines. Theoretical understanding in biology deserves the same place of prominence it already enjoys in physics[35,114,115].

The eight propositions discussed here are offered as possible ways in which we can expand the palette with which we paint our understanding of the living. I am sure there are many others, though in the end I think the most important conceptual principle of all is that nature is nature and does not care about our disciplinary boundaries — everything we have should be brought to bear on trying to understand the world around us.

The soul of physics: a philosophy of nature

In this special issue of *Current Biology* in the pages that follow, I hope that the readers will bear in mind a perspective in which physics is not so much a subject, but a style. What do I mean by that? Physics has its roots in natural philosophy, the expansive subject that has as its goal nothing less than to understand the natural world. Over time, that subject narrowed its purview to the idea that physics is the study of that part of the natural world that is investigated using the tools of physics — quantitative descriptions, a strict interplay between theory and experiment, and so on. But with the mind-boggling advances in the way we can observe and measure the living world that have been made over the last half century (to pick an arbitrary date), it is now possible to envision a description of life that obeys the mantra “quantitative data demand quantitative models”. In my subjective opinion, the most important path forward for the future of our understanding of life is the development of a proper role for theory in the great subject of biology. The articles that follow provide exciting examples of the ways in which the physico-mathematical mindset can help us better understand the answer to Schrödinger’s age-old question of “what is life?”.

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My referencing here is highly idiosyncratic. It is meant to be fun and interesting. It does not provide a scholarly interpretation of the literature. Rather, it is largely a reflection of my personal pleasure in reading the works of others that I share here in case readers wish to explore some highlights from my own reading list. The scholarly references are offered to precisely support particular points made in the article.

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Feature

Droplets in the cell or just a mirage?

A wave of new research on compartments in the cell called 'membraneless organelles' suggests that they are created through a process of phase separation, an idea from the early days of cell biology that has been revived. However, some question the biological relevance. **Cyrus Martin** explores the history and current debate.

It's difficult to pick up a biology journal these days without encountering the term 'phase separation'. In its most recent incarnation, phase separation is a leading candidate to explain how compartments smaller than organelles are formed. Initially applied to such things as nucleoli and a range of somewhat more mysterious 'membraneless organelles' in the cell, such as Cajal bodies and stress granules, we are now seeing claims that many other structures and compartmentalized processes, too, may be created through phase separation, leading to 'biomolecular condensates', another frequently used term. Included in this growing list is the centrosome, that huge protein complex responsible for building mitotic spindles, and even DNA-repair foci. The impact of the idea can clearly be seen by plotting how the number of articles with the term 'phase separation' in the title has grown over time. From 2010 to 2024, the number of such papers increased almost sixfold, far outpacing the overall growth of citations in general. You will see titles such as 'Role of liquid–liquid phase separation in cancer: Mechanisms and therapeutic implications', or, for example, 'Phase separation and inheritance of repressive chromatin domains'.

What exactly is meant by 'phase separation'? The example most often used is the separation of a mixture of oil and water into different layers, or the formation of an emulsion consisting of dispersed oil droplets. Turning to something more biological, when a protein becomes increasingly concentrated in a solution, there may be a point where weak, low-specificity interactions between protein molecules are favored over interactions with the solvent. In that case, the protein can adopt a distinct, high-density phase characterized by liquid droplets dispersed throughout the solvent.

Early observations of droplets and the evolution of life

The idea of droplets inside the cell is actually an old one. Many early cell biologists at the beginning of the 20th

Current Biology

Following the trends: Plotting the number of papers in PubMed with the term 'phase separation' in the title reveals the recent, rapid growth of the idea and its influence on cell biology.