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Key Issues Review

The hidden simplicity of biology

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Abstract

Life is so remarkable, and so unlike any other physical system, that it is tempting to attribute special factors to it. Physics is founded on the assumption that universal laws and principles underlie all natural phenomena, but is it far from clear that there are 'laws of life' with serious descriptive or predictive power analogous to the laws of physics. Nor is there (yet) a 'theoretical biology' in the same sense as theoretical physics. Part of the obstacle in developing a universal theory of biological organization concerns the daunting complexity of living organisms. However, many attempts have been made to glimpse simplicity lurking within this complexity, and to capture this simplicity mathematically. In this paper we review a promising new line of inquiry to bring coherence and order to the realm of biology by focusing on 'information' as a unifying concept.

Keywords: complexity, emergence, biological laws

(Some figures may appear in colour only in the online journal)

1. Introduction

Physics is founded on the assumption that universal principles underlie all natural phenomena. Although examples of individual physical systems may be very complex and intricate in their details, there is a widespread belief that simple mathematical laws operate at a fundamental level. The existence of such laws underpins the remarkable success of theoretical physics, which has impressive, high-precision predictive power. A stunning example is the theoretical prediction for the value of the anomalous magnetic moment of the electron, which has been confirmed by measurement to more than 10 significant figures [1].

Biology in its current state is very different. In biology the microstates are often highly unpredictable; there is nothing close to the predictive power of fundamental physics. Although Darwinian evolution serves as an over-arching statistical framework, it is not generally predictive—we are hard-pressed to calculate even basic parameters in biology, such as the mutation rate needed to properly standardize phylogenetic trees or identify where the root of the tree lies [2]. Where predictive power is found in biology, it is often in large-scale properties, for example homeostasis. Thus one can predict aggregate (macroscale) features but not those occurring at the lower levels. There is no 'theoretical biology' in the same sense as theoretical physics, because macro-level features of biological organization detailed to date are so far not known to be universal. Indeed, it is unclear whether any 'laws of biology' akin to the laws of physics even exist; if they do, they remain to be fully explicated [3]. It could be that biology is not ruled by universal laws, and is simply a vast catalogue of isolated special cases with at best some recurring themes and trends.

On the other hand, physicists are familiar with the fact that most of the simplification underlying our theories is not apparent on the surface. Superficially the physical world seems dauntingly complex. To be sure, some simplicity is apparent: for example, the patterns in snowflakes, the spherical figure of

the sun and the rhythms of the seasons. But the most powerful simplifications are abstract and generally hidden. Consider, for example, the crucial role of gauge symmetries in Maxwell's laws of electromagnetism, Einstein's general theory of relativity and in the standard model of particle physics. These symmetries are powerful ways to simplify and unify a bewildering array of natural phenomena, yet they were uncovered only in the past few decades and do not present themselves in any obvious way to the senses. Or, to take an even more abstract example, supersymmetry remains a popular simplification and unification in our theoretical description of nature, although so far it has remained completely hidden if it exists at all.

In this review we explore the possibility that biology, which is also bewilderingly complex on the surface, may likewise possess hidden abstract simplicity, awaiting discovery. As in physics, biology displays some obvious overt simplifications. The widespread appearance of bilateral symmetry, the spiral shapes of shells, Mendel's laws of genetics, the widespread appearance of fractal structures and the arrangement of leaves in Fibonacci series are some well-known examples [4]. But is this just the tip of an iceberg? In this review we explore the hypothesis that there may indeed be at least quasi-universal laws underlying biological organization—that is, that there may be as-yet unidentified forms of simplicity hidden in biological phenomena. Our focus will be on the concept of *information*, an abstract quantity that nevertheless seems to make a big difference to the way the world works. We posit that it will be in the realm of information theory and information dynamics that powerful new integrating principles of life will be discovered.

Whereas a physicist might describe a living organism in terms of entropy, molecular shapes, binding energy, etc, biologists typically use information language, for example, by describing genomes as 'databases' that get 'transcribed' and 'translated' according to a universal 'code'. Cells 'signal' each other. Sensory information gets processed in a variety of networks from gene regulation up to neural networks. Even on an ecological scale the web of life involves vast amounts of information sharing and processing.

Belief that progress in biology will come from shifting the conceptual basis from the traditional notions of 'form and function' and 'genotype and phenotype' to the abstract realm of information flow and management is becoming increasingly recognized [5]. If we could view the world through 'information eyes'—that is, see bits rather than matter—organisms would glow with a ferment of information processing: genetic information in nucleic acids and proteins, chemical signaling between cells and throughout the endocrine system, electrochemical activity in neural systems, interactions within ecosystems, cities, etc. It is true that complex non-living chemical networks would also reveal swirling information patterns, but we can hope that life might stand out as having distinctive organization in the flow of information. Adopting this view, living systems may be regarded as analogous to banks of electronic or computer circuitry, with cellular components treated as modules having logical functions, networked together to process information in specialized ways refined by natural selection [6, 7]. This is not to say that life is independent of its substrate, but instead that the key to understanding life might lie instead in studying how information interacts with the material world. Analyzing life's informational properties holds promise for turning biology into a quantitative science with real predictive power, akin to that of theoretical physics—or perhaps electrical and electronic engineering is a closer analogy. It may also advance our understanding of the origin of life and life on other worlds [8].

2. What is life?

In 1943, while World War II raged in Europe, Erwin Schrödinger, already well known as one of the founders of quantum mechanics, was sheltering in neutral Ireland, and so able to pursue his scientific interests undisturbed by military conflict. His deliberations resulted in a book called *What is Life*? [9], published the following-year, and according to folklore it exercised a huge influence on a generation of young scientists poised to make the transition from physics to biology [10]. In particular the science of molecular biology, still in its infancy in the 1940s, was ripe for discovery. Whatever the reality of the folklore, there is no doubt that Schrödinger's question was a profound and baffling one, and remains so today. The universe is full of weird and awe-inspiring phenomena, but life occupies a special place in the list that seems to deserve our attention. After all, it is from life that mind arises, and with that the very notion of a human being and the scientific investigation of nature. We are the product of life, and so it is no surprise that it exercises a special fascination for us. But just how peculiar is life, in fact? Might it be merely one particular quirky state of matter that attracts us because of its parochial significance? Can we even draw a line between non-living and living systems and assign different qualities to them in an objective way? And how did life get started in the first place?

A major distinction between the biological and physical sciences, and a stumbling block for addressing these questions, is the sheer complexity of life. Certainly, the diversity of functions and length and times scales of biological phenomena—ranging from protein signaling within cells, to quorum sensing among populations, to embryo development, to collective-decision making by eusocial insects, and even the organization of cities—leaves one baffled as to what universal law(s) could possibly underlie such far-reaching and diverse phenomena. Whereas the properties of systems typically studied in physics can often be reduced to the interactions of a few simple components, biological systems, by contrast, do not maintain their 'life-like' properties when reduced to their component parts. We therefore cannot take apart a bacterial cell, isolate its components, study them in isolation, and derive the behavior of chemotaxis, say, in the same way as we might take apart an atom and predict its properties based on reconstructing its electron orbitals from a few relatively simple principles. Without being able to reduce biological complexity to the interactions of a few key components, it is unclear how we might uncover any universal biological laws. And even in cases where non-living systems cannot be readily

reduced to the physics of their components, simplification may often be achieved by neglecting effects on certain length and/or time scales and focusing on the phenomenon of interest. Thus we can usually ignore atomic physics when treating the Young's modulus of a deformable solid or ignore Poincaré recurrences when dealing with the statistical mechanics of a gas on everyday time scales. But in biology, the behaviour of a system often depends on interactions over many disparate length and time scales. For example, the architecture of chromatin (the material carrying DNA) is highly dynamic and complex, but its mesoscopic organization at any given time may depend on effects operating on the length scales of individual genes (due to genetic switching) up through cells and tissues to the whole organism.

An early scientific attempt to capture hidden simplicity in biology was vitalism. Popular in the late nineteenth century, it posited that living organisms acquire their amazing properties by being infused with a sort of 'life force' or *élan vital*, a belief encouraged in part by the effects of the still-mysterious phenomenon of electricity on living organisms [11]. One champion of vitalism, Hans Dreisch, argued that a non-physicochemical force was the best explanation for how embryos develop and can recover their appropriate final form even when subjected to some mutilation [12]. In some respects, the life force is reminiscent of the luminiferous aether in physics. Popularly, vitalism, like the aether, is dismissed as pseudoscience today, but we have yet to demonstrate a quantitative alternative. The original motivation for vitalism was in fact a serious attempt to find hidden simplicity in biology. Had it been on the right track, one can imagine that the elusive and mysterious *élan vital* might, like the unseen electromagnetic fields also studied in the nineteenth century, conform to some sort of *mathematical laws* that would enable biologists to explain complex states of life and predict their properties in terms of the corresponding states of the invisible animating essence, just as we may today describe the output of a radio in terms of invisible electromagnetic fields.

Modern biology is formulated in a very different kind of framework, based not on mathematical laws describing unseen forces, as is often done in modern physics, but purely using Newtonian mechanics: cells resemble factories that contain much of the paraphernalia familiar to engineers—pumps, pulleys, rotors, levers, scissors, ratchets, etc. These components are molecular machines, powered by proton gradients across membranes and with the energy needed to make the machines tick stored in the molecules known as ATP. (For a comprehensive introductory review, see [13]). The lion's share of the work and the structural equipment is provided by proteins, which are assembled in nano-machines called ribosomes. The assembly instructions are coded in DNA, transcribed into RNA and delivered to the ribosomes. The cell is a community of mechanisms executing instructions stored at the molecular level, a story now well cataloged due to significant advances in the field of molecular biology.

Since Schrödinger drew attention to it over 70 years ago, scientific understanding of the nature of life has advanced enormously, and in recent years new clues to life's origin have been uncovered [14]. Yet it would be wrong to claim that we are on the verge of answering Schrödinger's question. Much remains murky and ill- defined. Many people working in the field have the sense that something important has been left out of account, perhaps something fundamentally new and therefore difficult. If only the problem could be re-cast within a new conceptual framework, then perhaps everything would fall into place. The history of science is replete with examples of how some sort of paradigm shift abruptly transformed understanding of stubborn mysteries and opened the way to rapid advances. One such shift was in fact quantum mechanics, which at a stroke paved the way to an explanation of atoms, molecules, chemical bonds, nuclear reactions, subatomic particles and much else.

Flushed with these successes it is no surprise that Schrödinger felt quantum mechanics might have the power to explain life too. It was a view shared by many of his distinguished quantum colleagues, such as Niels Bohr [15] and Werner Heisenberg [16]. Today, this view seems naïve. Evidence suggests that, here and there, certain quantum effects may play a critical role in biology [17, 18]. There is, however, no known 'life principle' flowing from the principles of quantum mechanics to suddenly turn biology into a predictive science like physics.

So what, then, is life? Seventy years after Schrödinger posed his provocative question we are now glimpsing not just an answer, but a wholly different type of answer from the one he envisaged. Life is a network of information processing, storage and management systems with mathematically distinctive properties. Like a bewildering electronic circuit board it may appear hopelessly complex at first sight, and a descent into the even more complex molecular details would prove mostly fruitless. But an electronic engineer, versed in the principles of circuitry and conversant with the logical architecture and information flow of the system, can give a clear account of what even a very complicated circuit is doing, and can fix it if something goes wrong [19]. So a future 'biological software engineer' will be able to study an organism's logical structure and explain what is happening at the global level. This engineer may even be able to work out what might go wrong in, for example, cancer, and fix it by repairing the informational circuitry.

The revolution in molecular biology in part triggered by Erwin Schrödinger in the middle of the last century now looks set to be followed by an equally dramatic revolution in systems biology that will change the whole character of the biological sciences and their relation to physics and chemistry, and perhaps finally answer the perennially fascinating question of whether or not we are alone in the universe.

3. Information: the language of life

Although an abstract concept, information has become so familiar that there is a temptation to treat it as some sort of ethereal substance. But this cannot be quite right, because each bit of information has to be instantiated in physical degrees of freedom: 'Information is physical!' as Rolf Landauer famously proclaimed [20]. So on the one hand, the dynamics

of information depends on the underlying dynamics of the physical degrees of freedom. On the other hand, in some circumstance (such as biology) it appears to take on 'a life of its own': philosophers describe it as 'an emergent property' [21]. In biology especially, explanations are usually couched in a language suggestive that 'information' itself has causal efficacy [22]. Thus DNA is often described as a blueprint or algorithm for building an organism, with the implication that the genome controls or supervises embryo development by exerting some influence over the course of events. The causal narrative becomes even more striking in the realm of neuroscience. For example, people often describe experiencing 'a train of thought' in which one thought or sensation from sensory input leads to a further thought in what is felt by a conscious being as a cause-effect relationship. A hard-nosed reductionist would ascribe a parallel chain of physical causation to all such examples. However, such is the complexity of biological matter that it would obviously be completely impracticable to re-cast these mental narratives in material terms alone, on a molecule-by-molecule basis. So, practical biology demands a rough-and-ready type of dualism—of *matter and information*—as a methodological necessity. In the absence of a unitary theory that encompasses both living and nonliving matter we are forced to adopt the information-matter duality as a pragmatic step, while remaining agnostic to the reductionist claim that all informational narratives are ultimately reducible to material causation.

To move beyond a purely descriptive analysis it is necessary to introduce some method of formalizing information content and flow. While the properties of matter have been quantified for centuries, information theory is a relatively recent development. It began in earnest with the seminal work of Claude Shannon in 1943 in which a quantity termed information (I) is closely identified with entropy [23]:

$$I(X) = -\sum_{x\in X} p(x)\log p(x) \tag{1}$$

where $p(x)$ is the probability for the random variable X to be in state x. Equation (1) is frequently referred to as Shannon entropy. Shannon was primarily interested in the problem of sending and receiving a message over a noisy communication channel and the Shannon entropy is often colloquially described as the degree of surprise you might experience at learning the outcome of an event—the more unlikely the event, the more surprised you feel at learning about it. Viewed in this light, the concept of information is closely related to reduction in uncertainty—the less uncertain an event is, the less surprised you are by the outcome of the event and the less information it contains. Clearly $I(X)$ is maximized when $p(x) = \frac{1}{n}$ for all $x \in X$, where n is the number of possible states x.

If X represents the microstate of a physical system, the mathematical form for Shannon entropy is directly related to thermodynamic entropy:

$$H(X) = kI(X) \tag{2}$$

i.e. here, k is Boltzmann's constant, which points to a deep connection between information theory and thermodynamics. There has been substantial work over the last several decades to make this connection more explicit [24, 25]. Schrödinger was aware of this link in his deliberations on biology, and famously coined the term 'negentropy' to describe life's ability to seemingly violate the 2nd law of thermodynamics (it doesn't really). Yet he felt that something was missing, and that thermodynamic considerations alone are insufficient to explain life (see [9]):

> *"…living matter, while not eluding the "laws of physics" as established up to date, is likely to involve "other laws of physics" hitherto unknown …"*

In what follows, we adopt a different approach and focus on the connection between information and the rather ill-defined concept of *causation*, as this has been much less thoroughly explored in the literature and thus represents a new frontier for physicists interested in entering the biological sciences.

The field of information theory developed over the past several decades has found applications to all areas of science and engineering, and establishes the basic framework for quantifying information. In this paper we make no attempt to review the (vast) field of information theory as such, but restrict attention to the quantification of the flow of information in complex systems and its subtle relationship to patterns of causation. These are two aspects of information theory that most illuminate the central puzzle of biology, namely, what, precisely, are the physical properties that distinguish living from non-living complex systems?

3.1. Quantifying 'vital' bits

Although informational analogies are widely applied in biological sciences, there is no clear consensus on the ontological status of information in biology, or even precisely what is meant by the concept of 'biological information' [26], which appears to not be fully encompassed by Shannon's definition. One of the most important hallmarks of life (discussed in detail below), which is also one of the most perplexing from the perspective of physics, is that biological systems exhibit *functionality*[4]. That is, we tacitly assume that biological systems and structures are 'for' something; for example, eyes are *for* seeing, wings are *for* flying, and ribosomes are *for* making proteins. By contrast, in physics we would not say that an electron, or a turbulent eddy, is 'for' anything. The Shannon definition of information is purely syntactic and directed to quantifying the relationships between individual characters used to construct a signal. It therefore cannot capture the notion of being 'for' anything as it is entirely agnostic about the content of the message received [27]. By contrast, in biology the semantic content of the message, which concerns its meaning, does *prima facie* seem to matter.

[4] By the very nature of describing function, one often utilizes terminology associated with purpose, a teleological concept riddled with controversy. However, as Dawkins has stressed (see [50]), the distinctive feature of Darwinian evolution is precisely that it can mimic design, and give the *appearance* of purpose. Thus we would expect highly evolved organisms to look highly designed, even if the 'designer' is natural selection.

One widespread measure applied to biology is *mutual information*

$$I(Y;X) = \sum_{y_n, x_n} p(y_n, x_n) \log_2 \frac{p(y_n, x_n)}{p(y_n)p(x_n)}, \quad (3)$$

which quantifies the average information in a variable Y about another variable X, where $p(y_n, x_n)$ is the joint probability of the events y_n and x_n. Examples of the application of mutual information in biological modeling include quantifying the correlation between the information content of genomes and their environment [28], between molecules within the cell [29, 30], and between early life replicators [31] and their environment.

However, mutual information suffers from a major shortcoming in that it is not directional: it says nothing about which event preceded the other and as such can say nothing about the directionality of information flow or about causation. Nor does it address the all-important issue of functionality. Mutual information could not discriminate between claiming, for example, that a wing is 'for' flying or that flying is 'for' the wing, only that wings and flying are correlated[5].

Schreiber corrected the directionality problem by introducing the concept of *transfer entropy* for events separated in time [32]. Transfer entropy quantifies the extent to which knowing the state of one entity (the 'source') at a certain time assists in predicting the state of another entity (the 'destination') at a later time, over and above what we could have predicted by knowing the past of the destination states.

The formal definition of transfer entropy is

$$T_{Y\to X}(k) = \sum_{x_{n+1}, x_n^{(k)}, y_n} p(x_{n+1}, x_n^{(k)}, y_n) \log_2 \frac{p(x_{n+1}|x_n^{(k)}, y_n)}{p(x_{n+1}|x_n^{(k)})}, \quad (4)$$

where y and x denote the source and destination respectively and the subscripts denote the time steps. The label k denotes the number of past states of x taken into account in the history leading up to the time step of interest. The history length k is a free parameter; typically one considers the limit $k \to \infty$, although for biological systems we have suggested that important aspects of the systems dynamics might be captured by considering finite k [33].

One can view the transfer entropy as conditional mutual information $I(Y_n; X'_{n+1}|X_n^{(k)})$. The basic idea is that the prediction of the next value for a given variable at step n, given knowledge of its past k states, could be improved by taking account of the state of other variables at step $(n-1)$. If that is the case, then in some sense information has been transferred between the two variables under consideration. If the correlation is high, it implies that knowledge of the other source variable leads to better prediction of the state of the destination variable at step n. Since it quantifies information transferred from a source to a destination, transfer entropy may be interpreted as a measure of 'information processing' [34].

[5] Saying that flying is for the wing is of course nonsensical when you know the meanings of the words, but that is part of the problem to be solved—we do not know how to quantify meaning, which would require a measure that includes the semantic content of a message.

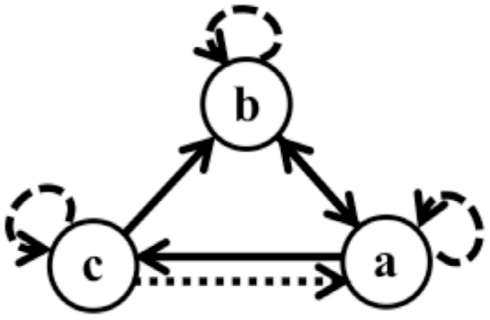

Figure 1. Three-node Boolean network for illustrating the concept of transfer entropy. Dashed lines indicate inhibition links (each node has one self-inhibition link) and solid lines indicate activation links.

Transfer entropy has quite general application to physical and biological systems, but in this review we restrict attention to *networks*, which are relatively easy to analyze and yet accurately model many biological processes. To illustrate the general idea we use the simple three-node Boolean network shown in figure 1.

In the diagram the links between nodes denote a direct causal interaction, either inhibition (dashed edge) or activation (solid edge). In the network shown all nodes causally interact with all other nodes, either via activation or both activation and inhibition. The nodes a, b, and c can take on values of '0' or '1' ('off' or 'on'). For purposes of illustration we choose the following Boolean update rule for the states of nodes:

$$S_i(t+1) = \begin{cases} 1, & \sum_j a_{ij} S_j(t) > 0 \\ 0, & \sum_j a_{ij} S_j(t) < 0 \\ S_i(t), & \sum_j a_{ij} S_j(t) = 0 \end{cases} \quad (5)$$

where the weights a_{ij} for activation and inhibition are $a_{ij} = 1$ or $a_{ij} = -1$, respectively. We also arbitrarily pick the initial state $\{1, 1, 1\}$ (all nodes activated) and proceed in 10 discrete time steps using the update rules in equation (5). Proceeding step by step we obtain the time series of states shown in table 1. The states converge to a fixed attractor at $t = 3$ steps, which then repeats every three time steps.

There are $2^3 = 8$ possible initial states, each giving rise to a similar 3×10 table of '1's and '0's. These tables can be examined for patterns, from which we may compute probabilities (using frequency distributions) in order to work out the transfer entropy between pairs of nodes. Since this example is a small, deterministic network, all possible trajectories, and thus all possible patterns, may be readily generated. Denoting by P the total number of patterns counted, we see that $P = 2^3 \times (N - k)$, where $N = 10$ is the total number of time steps, and k is the history length we choose to take into account. The probability for a particular pattern to occur is then defined as its total number of occurrences over all trajectories, divided by P. Consider, for example, node b. The three-step historical sequence $b_n(3) = (1, 1, 1)$ occurs just once in table 1, but when the full set of 8 tables is examined it is found

Table 1. Time series of node states for the three-node network shown in figure 1 evolved according to the Boolean update rule in equation (5), initialized in the state (1, 1, 1).

Time step	Node a	Node b	Node c
1	1	1	1
2	0	1	1
3	0	1	0
4	1	0	0
5	0	1	1
6	0	1	0
7	1	0	0
8	0	1	1
9	0	1	0
10	1	0	0

to occur 3 times. Since $k = 3$ and $N = 10$, the relative frequency of $b_n(3) = (1, 1, 1)$ is therefore $p(b_n(3)) = 3/56$.

Turning now to transfer entropy, recall that it quantifies the degree to which adding knowledge of the state of node a, or of node c, at the preceding time step $(n - 1)$ might reduce the uncertainty about predicting the next state of b. We first consider information transfer from $c \to b$. In two out of its three occurrences $b_n^{(3)} = (1, 1, 1)$ is followed by $b_{n+1} = 0$; in both cases $c_n = 0$. Therefore the joint probability (frequency) of $(c_n, b_n^{(3)}) = (0, (1, 1, 1))$ to occur is $p(0, (1, 1, 1)) = 2/56$. Similarly, the joint probability (frequency) of $(c_n, b_n^{(3)}) = (1, (1, 1, 1))$ is $p(0, (1, 1, 1)) = 1/56$. To compute the transfer entropy from $c \to b$ it is necessary to sum over all eight possible historical sequences of length $k = 3$ (e.g. $(1, 1, 1), (1, 1, 0), (1, 0, 1), (1, 0, 0), (0, 1, 0), (0, 1, 1), (0, 0, 1), (0, 0, 0)$) and over both '0' and '1' for the preceding state of c, assigning probabilities to the relative frequencies of each pattern occurrence. This summation yields $T_{c\to b}(k = 3) = 0.049$ bits. The number 0.049 is a measure of how much information (in bits) is transferred from $c \to b$ as a result of the network's dynamics. A similar calculation shows that the transfer entropy from $a \to b$, $T_{a\to b}(k = 3) = 0$, so that *no information is transferred* from $a \to b$ in the execution of this network's dynamics.

The foregoing very simple example highlights an important recurring theme of information flows in complex systems. First, it is computationally very demanding to calculate information measures, a burden that escalates sharply with network size. Second *direct causal interactions do not necessarily imply correlation nor does correlation necessarily imply causal interaction* (we will see an explicit example of the latter below in section 5.1). For the two cases considered, information transfer from $a \to b$ and $c \to b$ is only non-zero for the latter, despite the fact that both involve direct causal interactions between pairs of nodes. It is therefore not just causal structure (e.g. whether two nodes are connected by and edge or not) that mediates the flow of information in a network, but also the wiring of the entire network (i.e. its topology) and the dynamics (as captured in the time series of states) [34]. We will encounter this again in discussion of the potential unique features of biological organization discussed below.

3.2. Correlation ≠ causation

The fact that the causal and informational narratives do not generally coincide in network dynamics is an illustration of the *information-matter* duality concept we introduced at the beginning of section 3. This raises the fundamental question of how the informational dynamics relates to the causal dynamics of the network. Are there any general principles that might apply to all biological systems? For a network such as that in figure 1, causal connections are completely specified by the edges between nodes. Some, but not necessarily all, of these edges mediate information transfer as highlighted in the above example. Because transfer entropy can also be non-zero between nodes that are *not* connected by an edge, it captures a more distributed notion of causation in a network. In this respect it is reminiscent of the phenomenon of stigmergy, common in eusocial insects, where interactions are mediated by traces left in the environment [35]. For example, ants may leave chemical trails that affect the behavior of other ants in such a manner that the colony displays coherent activity even though individual ants are not *directly* interacting with each other through physical contact, but instead share a response to a common causal signal (the pheromone) [36].

In general, when there is substantial information transfer that is not mediated by a direct causal interaction, it is a sign of entrainment, or cooperative behavior, where collective modes of the system dominate over individual modes in shaping the informational dynamics—a concept with a very old pedigree in physics and engineering [37]. Famous examples are the observation by Christiaan Huygens that nearby pendulum clocks tick in synchrony. A more modern example is the laser, in which photons from vast numbers of atoms become phase-locked to produce coherent light. In biology, various circadian rhythms lock onto the day-night cycle. Cooperative phenomena of a more complex nature have been intensively studied in physics under the encompassing title of 'synergetics' [38].

Distributed correlations picked up by transfer entropy often manifest the oft-quoted mantra '*correlation does not imply causation*'. There have been various attempts to disentangle correlation and causation, especially as applied to complex networks [39]. Any such discussion requires an explicit notion of causation, with attempts to quantify this seemingly murky concept presented in fields as diverse as philosophy [40], biochemistry [41] and economics [42]. Many of these analyses appeal to the notion of a *causal intervention* [43] in which a small perturbation to the system produces measureable downstream consequences. Thus if a system X is causally linked downstream to a system Y, then a perturbation of the state of X will produce a knock-on change in system Y. A very practical example comes from the field of cancer therapy, where a small molecule drug might be used to block a cell surface receptor, or a key point in a chemical pathway within the cell, with a view to inactivating some downstream process, such as the production of cellular growth factors.

Using an interventionist approach, the causal mechanisms of a system may be investigated by constructing the *interventional conditional probability* $p(X|\widehat{Y})$, which is the probability

distribution over variable X when one imposes on the variable Y the fixed value $\widehat{Y}$. In general, $p(X|\widehat{Y})$ is *not* the same as the conditional probability $p(X|Y)$, where for the latter Y can take on any value. For example, consider two variables X and Y that are each separately affected by a third variable C. In this case X and Y are correlated as a result of being under the influence of a common cause, i.e. $p(X|Y) \neq 0$. However, pinning the value of Y to $\widehat{Y}$ cannot affect X (as Y and X are not causally connected), so $p(X|\widehat{Y}) = p(X|Y)$, that is, no change in the conditional probability distribution over variable X arises due to manipulation of Y.

The notion of causal information flow was recently placed on a rigorous footing by Ay and Polani [44], who adopted the following definition:

$$I_p(Y \to X|\widehat{S}) = \sum_s p(s) \sum_y p(y|\hat{s}) \sum_x p(x|\hat{y},\hat{s}) \log \frac{p(x|\hat{y},\hat{s})}{\sum_{y'} p(y'|\hat{s}) p(x|\hat{y}',\hat{s})}. \quad (6)$$

where X again is the destination and Y the source random variable. Here, s is a set of other variables in the system that must be 'blocked' by intervening on the system to set their value in order to isolate the contribution from Y to X. Although Ay and Polani called their measure 'information flow', for purposes of discussion herein we prefer to use the term causal flow to refer to equation (6) to avoid confusion with information transfer and other non-interventionist concepts of information. Causal flow quantifies the deviation of the destination X from causal independence on the source Y, when conditioned by intervening on all other possible contributors S (in a complex network these would be other nodes in addition to Y that are directly connected to X via an edge). Ideally, S should include all other potential causal contributors to X, to isolate the direct causal contribution from Y, although this is difficult to do in practice if the full causal structure of the system is not known *a priori* (which is often the case). The formula for information flow looks structurally very similar to that of transfer entropy (and indeed both are directional information measures). However, the key difference is that transfer entropy is based on standard conditional probabilities while information flow is based on *interventional* conditional probabilities.

A detailed analysis to untangle the distinctions between information transfer and causal information flow on a local scale has been provided by Lizier and Prokopenko [39]. Utilizing elementary cellular automata (CA) as a model system to rigorously examine the properties of both measures in a comparative analysis, they demonstrate that transfer entropy accurately tracks emergent structures, such as gliders, which are believed to play an important role in the intrinsic computational properties of CA, whereas these structures are *not* picked up by causal flow. They conclude that while causal flow may be used to capture causal structure, transfer entropy is better suited to describe emergent computation (information flows) on that causal structure. Thus, causal flow and information transfer appear to be describing informational structure at two distinct levels of organization, at least for the simple CA models examined by Lizier and Prokopenko. While cellular automata are a far cry from biological complexity (see also section 7.2), these considerations illustrate that there is much to be gained by studying in parallel the causal and informational structure of complex systems.

Summarizing the results reported in this section, the behavior of living systems can be characterized by changing patterns of information and changing patterns of causation. The question then arises of the relationship between them. The foregoing network examples show that there can indeed be differences in the two patterns, which prompts us to ask about the status of informational narratives. Such narratives undoubtedly have explanatory value, but can we go beyond pragmatics and uncover truly law-like, albeit emergent, features of information flows? If the mapping between information flow and causal flow were exact, then information would be merely an epiphenomenon with no fundamental ontological status. But if it is not exact, we would like to know if there are general laws describing this linkage, laws that might serve for biology the role that Newton's laws serve for physics. These remain open questions.

4. The hallmarks of life

> '*How remarkable is life? The answer is: very. Those of us who deal in networks of chemical reactions know of nothing like it… How could a chemical sludge become a rose, even with billions of years to try?*'
>
> George Whitesides [45]

Biological systems distinguish themselves from complex nonliving systems by a variety of hallmarks (see [8]). Most are associated with the unique informational properties of biological systems that sets them apart from other 'complex' states of matter, as discussed in the previous section. The hallmarks center on the presently murky, but potentially deep, connection between information and causation in living matter. Many of these hallmarks may turn out to be different descriptors of the same physical process(es) pointing to a hidden simplicity in the structure of living systems that remains to be fully explicated. Here we briefly review each of these hallmarks in turn, before considering explicit examples of where some of these concepts have been applied to biological systems to provide insights into the physics of life (see table 2 and [8] for an extended discussion).

4.1. Global organization and the illusion of design

Biological systems are widely regarded to be distinctive in their emergent or collective properties [46]. One need only look at a school of fish [47], the organization of Wikipedia [48], or the packing of a nucleosome to see examples of how local rules can lead to complex collective patterns and collective decision-making. The distinctive relationship of the whole to its parts displayed by living organisms has been the subject of commentary since at least the eighteenth century [49]. As Dawkins has stressed, the *appearance* of design is probably the most distinctive hallmark of life [50]. It may be that this global coherence and design-like organization arises

as a result of the patterns of information flows in biological systems. However, this remains to be quantified as a universal principle of biological organization.

4.2. Information as a causal agency

As noted above, there appears to be a deep connection between information and causation in biology, as most prominently captured by the notion of 'function'. If information does in fact play a causal role in the dynamics of biological systems, then a fundamental understanding of life as a physical process has the potential to open up completely unexplored sectors of physics, as we know of no other class of physical systems where information is necessary to specify its state.

4.3. Top-down causation

To short-cut the complexity inherent in biology, it is sometimes fruitful to embrace the concept of top-down causation [51, 52]. Reductionism holds that the behavior of a physical system can be traced back to the behavior of its components. That works well in physical systems that permit a separation of scales, e.g. explaining the gas laws based on averaged molecular motions. But, as we have already stated, living organisms do not generally permit this layer-by-layer decomposition of causation. Indeed, the very term 'organism' embraces the concept that the entity as a whole possesses an agenda ('calls the shots') and that the components of an organism are often subordinated to the larger unit. Thus organisms deploy a variety of regulatory mechanisms to control their components, such as when a gene is activated by a cell because a certain protein is needed in response to a change in its environment. A well-known example is when a starving bacterium switches on an SOS response that elevates its mutation rate [53]. In cases where the simplest description is to attribute the cause of a change to a macro-system (e.g. a tissue, a cell, a mitochondrion, a chromatin cluster…) and the effect is manifested in a micro-system (e.g. a gene is switched on), the term 'top-down causation' is used. It is a tacit acknowledgement that collective or global degrees of freedom have meaningful causal efficacy over microscopic degrees of freedom. It may then be said that the properties of the macro-system emerge from, are consistent with, but are not reducible to, those of the component micro-systems. If it turns out in principle to be the case that biological systems are fully reducible to known physics, this likely won't hold much utility as it is often the higher-order properties we are interested in manipulating—for example, reverting the phenotype of a cancerous cell to a healthy one. The mechanisms through which top-down causation, if indeed it is a real and not just apparent property of nature, could operate in biology would most likely be through information (in an as yet unspecified manner) acting as a causal agent.

4.4. Analogue and digital information processing

Life uses both analogue information (e.g. chemical gradients in embryo development), and digital information (e.g. the digital sequence of DNA and the ubiquitous use of logic gates). The coupling of these two forms of information processing is likely essential to controlling the flow of information within biological systems. Digital information, in particular, is argued to be essential to life, and more specifically heredity, due to the necessity for error-correction [54]: and to reliably propagate information under laws of physics that do not include the design of the organism whose blueprint is inherited [55].

4.5. Laws and states co-evolve

Self-reference, as occurs when a sentence, idea or physical system refers to itself, is often noted as one of the most distinctive features of life and mind [8, 56–61]. Self-referential statements such as 'This sentence is false' are paradoxical and their analysis led to a revolution in our understanding of logic with Gödel's incompleteness theorem [59]. However, although examples of self-reference abound in biology—from formal language (a biological construction) to the interior architecture of the cell (e.g. in the feedback between expressed genotype ↔ phenotype), we do not yet have a clear picture of how self-reference could be consistent with the underlying physical account of living systems. Self-referential statements may be manifested in dynamical systems with state-dependent rules [60, 61], where the update rules are not fixed, but instead change as a function of the current state of the system (for example, in biological systems when the level of gene expression in turn dictates the turning on and off of genes), such that laws and states co-evolve. We shall return to this important topic in section 7.2. Dynamical rules that are functions of states (and therefore are time-dependent) stand in stark contrast to four centuries of science describing the world in terms of initial states and immutable laws of motion. If state-dependent dynamics plays a foundational role in living systems it implies (as Schrödinger mused) that there may indeed be as yet-uncharacterized 'other laws of physics' at work in biology.

4.6. Logical structure of a universal constructor

von Neumann was one of the first to address the problem of biological self-reproduction (and in particular how a machine could emulate it) with his formulation of a universal constructor (UC) [62]. Based on Turing's notion of a universal computer, which can compute any computable function, a UC can, in principle, construct any physical object, within a given universality class of objects, when supplied with sufficient resources. In order to specify which physical system to construct, the UC must be supplied with 'instructions' that permit the construction of that object from elementary operations (those permissible by the laws of physics). Self-reproduction occurs when those instructions specify how to construct the UC itself (and thus are necessarily self-referential). The logical architecture of the cell has been equated to that of a UC on numerous occasions (see for example [55]), however it remains an open question how directly the abstract concept of a UC maps to cellular function, and whether other biological systems might be equated to UCs.

4.7. Dual hardware and software roles for the genetic material

An important feature of von Neumann's concept of a UC is that the information content, which is necessarily instantiated in matter, must play a dual role—as both instructions to be read-out to specify the construction of the UC, and as a template for the blind copying of the information contained—in other words, it must act both as a *software* program to be read-out, and as *hardware* to be replicated. This duality is well represented in DNA, which participates in two distinct processes. In the first, coded base-sequence instructions for making proteins are transcribed; this is the software aspect. In the second, the DNA molecule is blindly copied during the replication process at the end of the cell cycle; this is the hardware aspect. This logical structure is necessary to avoid the paradoxes of self-reference—if it were not the case the instructions would need to contain a copy of the instructions, which in turn would also need to contain a copy of the instructions, *ad infinitum*. The logical architecture of a UC therefore provides an example of how physical systems can instantiate self-referential logic.

4.8. Non-trivial replication

Self-replication by a UC, which requires implementation of software (instructions) in addition to copying hardware, should be contrasted with replicating hardware alone. This distinction is often cast as one between trivial and non-trivial replication [63, 64]. Trivial replicators are physical systems such as crystals, RNA templates, or Penrose blocks [65], whose replication is dictated solely on the physical (and chemical) properties of the environment—the hardware aspect. As such, only a very limited set of objects is constructable, as dictated by the environmental context (e.g. pH, availability of free monomers, temperature, etc). By contrast, non-trivial replicators utilize a 'program' specifying which members, among a universality class of objects, is to be constructed—the software aspect. Obviously non-trivial replicators are far more versatile and powerful than trivial replicators.

4.9. Physical separation of instructions (software) from the mechanism that implements them

A feature distinctive to non-trivial replicators is that the software is stored in a genetic substrate (e.g. DNA in cells or a 'tape' in the UC), which is separated from its physical implementation, as read out by the constructor (cellular machinery). This separation of software from the substrate it controls is a necessary pre-condition for top-down causation to operate in biological systems to avoid issues associated with supervenience [66].

Although there is some overlap among many of these hallmarks, the concept of information provides a powerful unifying framework, whether applied in a narrow pragmatic sense or as a truly novel ontological category at the heart of science.

5. The Logic of Life

Although an electron may not be 'for' anything, a transistor or a logic gate regulating the flow of electrons in an electronic circuit certainly is. So we readily recognize functionality emerging at the macro-level in electronics and computer science. In this case, of course, the function or purpose of the component has indeed been deliberately designed (by an electronic engineer), but nonetheless these are still physical systems. Taking the *appearance* of design as a manifestation of the hallmarks of biology [50], the conceptual overlap, or analogy, with electronics and computing looks significant. To take but one example, there is a strong analogy between the evolvability of programmable electronic circuits and that of protein circuits as they are found within cellular 'hardware' [6, 7]. The 'circuitry' connection is a view well captured in a futuristic look at biology by Nurse, in a paper entitled '*Life, Logic and Information*' [5].

> *"We need to describe the molecular interactions and biochemical transformations that take place in living organisms, and then translate these descriptions into the logic circuits that reveal how information is managed. This analysis should not be confined to the flow of information from gene to protein, but should also be applied to all functions operating in cells and organisms".*

While a comparison of an organism and a human-designed physical system should be treated as only an analogy, it is clearly a very useful one, inasmuch as it permits the development of simple mathematical models of organisms that capture the essential functionality without the need to incorporate the vast and messy complexity present at the sub-component level. This systems view of life complements the more overtly reductionist approach of molecular biology [67].

In his visionary article, Nurse points out that the key to making progress along the foregoing lines is to focus on the concept of *information* as we do here. As explained in the foregoing sections, the use of hardware and software language to describe the workings of a computer are regarded as complementary, not contradictory. So while a physicist may explain very well the workings of a gate or a memory element in terms of condensed matter physics, such an explanation is of little use to someone who wants to know how *Windows* works or why the use of the 'Save' command sometimes causes a program to crash. Perfectly satisfactory explanations for the latter phenomena may be provided, however, by a computer scientist or a software engineer. Thus, by analogy with the world of computing, we call the informational description of biology 'the software of life' to stand alongside the more familiar physical morphological features, which correspond to hardware.

5.1. Biological circuits

As we pointed out above, one of the hallmarks of life is that biological information comes in both analogue and digital form. An example of analogue information is morphogens—continuously variable chemical gradients that control the development of the embryo [68, 69]. It has recently been discovered that patterns of electric membrane potentials also serve as morphological templates in 3D space [11]. Digital information storage is most familiar from base-pair triplets in

DNA, and the processing of this (coded) information via RNA and ribosomes is a defining characteristic of life as we know it. It seems very likely that it would be a hallmark of any form of life, as digital information is robust against perturbations and readily permutable to attain the variation essential to evolution as well as allowing accurate error-correction. Whether digital information is necessarily implemented in polymers is less clear; there seems to be no fundamental reason why it could not be stored in two dimensions (analogous to a compact disk) or even three dimensions—for example as occurs in peptide β-sheets [70]. The example of peptide assemblies highlights that digital information processing is by no means limited to DNA. While most biological information-processing components are not strictly digital in their physical operation, in many cases their logical function—which is often all that really matters—can be well approximated to the type of digital logic gates familiar in electronic engineering and computing. Thus there are well-known examples of AND, OR and other logic gates utilized even in bacteria, and extensive use of other familiar engineering functions such as feedback, feed-forward and time-delay control [6]. Genes may produce proteins that enhance or inhibit the expression of other genes, forming networks analogous to electronic circuit boards [71].

Many efforts in studying the circuitry of life have focused on 'motifs', or recurring patterns in the connections of edges among nodes. Motifs that are found in natural networks with greater frequency than in random networks are called *network motifs*. Detailed studies of network motifs have been performed on a number of systems from transcription networks to ecosystems and the Internet [72]. Transcription networks, for example, were shown to include a three-node 'feed-forward loop' and a four-node 'bi-fan', which show statistically significant enhancements in their frequency for biological transcription networks, as compared to their random network counterparts. Analogous analysis of '*informational motifs*' that a play a prominent role in information storage or processing within a network, to compliment recurring network motifs in the hardware, is currently in its infancy due to the challenge of assigning information processing and storage capabilities to local topological structures (in the absence of running their dynamics which is computationally intensive). However, some progress is being made in analyzing motifs associated with the storage of information [73], which could provide a fruitful line of inquiry if applied to biological networks.

Boolean network models in particular have proved useful for studying a variety of biological systems to uncover the operation of life's circuitry. A few examples are models of the genetic regulatory networks (GRN) underlying flower development in *A. thaliana* [74], the cell-cycle network of the budding yeast *S. cerevisiae* [75], and mammalian cortical development [76], as well as gene regulatory networks determining embryonic segmentation in *D. melanogaster* [77]. While there are minor differences among these models, such as the specifics of the updating rule or the number of possible states for a node, all these Boolean networks share a number of important properties. Among these, their central utility is in a large part attributable to the fact that biological systems seem amenable to the simulation of their basic dynamical behaviour and function in terms of logic operations and discrete modules, that is, without requiring detailed knowledge of the underlying kinetic parameters.

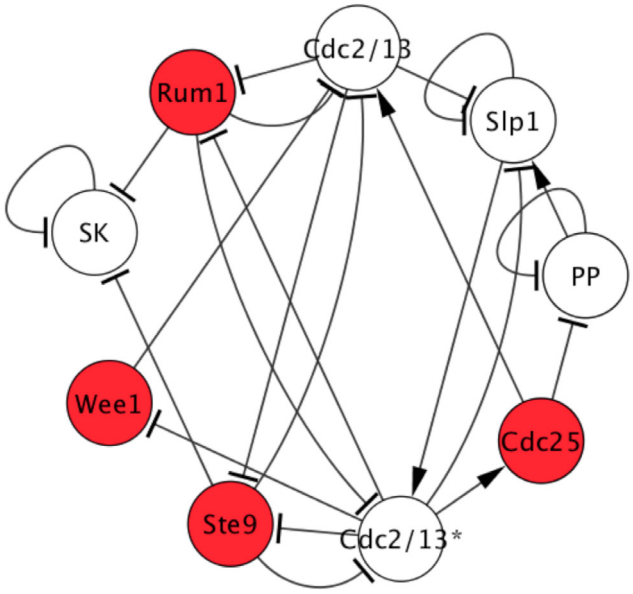

Figure 2. The Boolean network model of the gene regulatory network of the fission yeast *S. Pombe* cell cycle. Nodes and edges represent regulatory proteins and their causal interactions, respectively. Red nodes are components of the control kernel (see text). Figure adopted from [81]. Copyright 2015, The Royal Society Publishing.

Perhaps the most complete example of a biological circuit characterized to date is the genetic regulatory circuit for sea urchin embryo development, which has been cast in a predictive Boolean computational model that predicts the states of individual genes through the process of development (it is an open question how gene expression patterns ultimately map to morphological pattern formation, which also involves a variety of external cell-to-cell and environmental signaling) [78]. The model accurately predicts gene expression patterns up through gastrulation of the embryo, even predicting the correct sequence of events when the network is perturbed. The success of this work in predicting gene expression patterns demonstrates that models focused solely on the circuitry of life, and not on the substrate, can nevertheless accurately capture important aspects of biological function.

A simpler and well-characterized example of a Boolean network model for biological function is the cell-cycle regulatory network of the fission yeast *Schizosaccharomyces Pombe* [79]. The 'circuit diagram' is shown in figure 2, including the so-called *control kernel* nodes that play a special regulatory role (see section 6) [80].

In the figure, nodes represent genes (or equivalently their protein product) involved in the regulation of cell cycle function. They may take on a value of '1' or '0', indicative of whether the given gene is expressed or not (protein is present or not). Edges represent causal biomolecular interactions between two proteins, which can either activate or inhibit the activity of individual proteins. The successive states S_i of node i are determined in discrete time steps by the updating rule, which is applied synchronously to each node in the network:

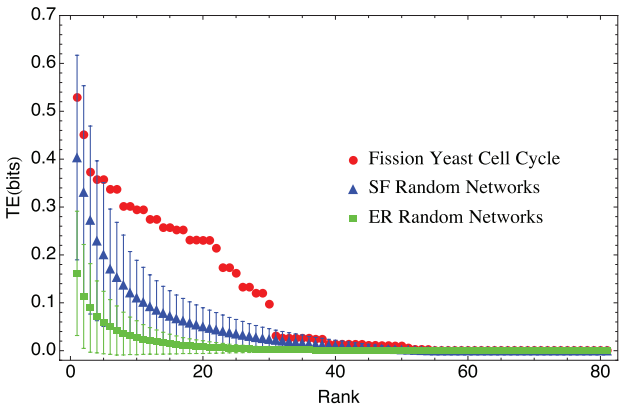

Figure 3. Scaling of information processing between pairs of nodes for history length $k = 2$ for the Boolean network model of the fission yeast cell cycle regulatory network (red), and ensembles of scale-free random networks (blue) and Erdös–Rényi random networks (green). Ensemble statistics are taken over a sample of 1000 networks. The y-axis and x-axis are the TE between a pair of nodes and its relative rank, respectively, over all network pairs. Figure adopted from [81]. Copyright 2015, The Royal Society Publishing.

$$S_i(t+1) = \begin{cases} 1, & \sum_j a_{ij} S_j(t) > \theta_i. \\ 0, & \sum_j a_{ij} S_j(t) < \theta_i. \\ S_i(t), & \sum_j a_{ij} S_j(t) = \theta_i. \end{cases} \quad (7)$$

where a_{ij} denotes weight for an edge (i, j) and θ_i is threshold for a node i. This rule table is similar in structure to that of equation (5) (both examples involve Boolean update functions at discrete time steps) but it differs in the assignment of threshold values. The threshold for all nodes in the network in figure 3 is $\theta_i = 0$, with the exception of *Cdc*2/13 and *Cdc*2/13*, for which it is $\theta_i = -0.5$ and $\theta_i = 0.5$, respectively. For each edge, a weight is assigned according to the type of interaction: $a_{ij}(t) = -1$ for inhibition, $a_{ij}(t) = 1$ for activation and $a_{ij}(t) = 0$ for no direct causal interaction. Applying the rules in equation (7) step by step to the network in figure 2 accurately reproduces the pattern of the expression states of the individual genes in this network through the several phases of cell cycle division.

The yeast cell cycle network is not arbitrary, but has evolved to be robust against perturbations (here we specifically focus on perturbations in the gene expression pattern, as captured by the state configuration of nodes, which take on values of '0' and '1'). This property is manifested in the shape of the network's attractor landscape, which has been charted by initializing the network in every possible state and running the dynamics until the network converges to an attractor. In the fission yeast cell cycle the attractor landscape has been shown to be dominated by the biologically functional attractor, corresponding to the stationary G1 resting phase of the cell: for this network 73% of all states will eventually converge to this single state. Similar features have been observed for the budding yeast cell cycle network, where the biological pathway is also a globally attracting trajectory of the network's dynamics [75].

Another feature that has generated much interest in studies of attractor landscapes of gene regulatory networks is the possibility of critical behavior. In particular, the distribution of avalanches in gene expression for knockout experiments—where genes are systematically removed from an organism—were shown to follow the same distribution as those for random Boolean networks in the critical regime between ordered and chaotic dynamics [82]. A more recent example of criticality comes from studying gene expression in macrophages, a type of white blood cell, where it was shown that macrophage gene regulatory dynamics are indeed critical [83]. Separate work on information processing in random Boolean network models has revealed that criticality corresponds to an optimal balance of information processing (measured by transfer entropy) and storage (measured by a related quantity called 'active information') [84], suggestive that perhaps biological systems are 'living at the edge' due to optimization of information management.

6. Scaling laws

So far we have focused on the local causal structure of biological networks, as captured by 'wiring diagrams' and network motifs. But biological systems also display common global features, hinting at universal laws underlying biological organization. One example concerns scaling relationships of the form:

$$Y(\lambda N) = \lambda^{\beta} Y(N) \quad (8)$$

where λ is an arbitrary scaling parameter, N is typically a measure of the size of the system, and Y measures a property characteristic of the system. Thus the scaling relation provides a direct mapping from the value of the parameter of interest, Y, for a system of size N, to the value of the same parameter measured on a system of size λN. The scaling $Y(\lambda N)/Y(N)$ is then parameterized by a single dimensionless number, the scaling exponent β. A simple solution to equation (8) is the power law relationship

$$Y = \alpha N^{\beta}. \quad (9)$$

Familiar examples from physics include critical phenomena near phase transitions, where physical properties such as heat capacity, correlation length, and susceptibility all follow power-law behavior [85].

An important feature of scaling laws is that they exhibit the property of scale-invariance, or self-similarity across scales, indicating that it may be possible to understand seemingly complex phenomena in terms of the composition of relatively simple interactions. Of special interest in biological networks is the widespread appearance of scale-*free* topology, in which a small subset of nodes possess a much higher connectivity than average [86]. Mathematically the scale-free property is expressed by the way that the fraction $p(k)$ of nodes having k edges decays as a power law: $p(k) \propto k^{-\gamma}$ (with γ often between 2 and 3 for biological and technological networks) [87, 88]. Scaling relations have been studied in phenomena as varied as the wealth of cities [89], metabolism [88], and neural systems [90].

Another scaling relationship of special interest that seems to be widespread in biological systems are the so-called allometric scaling relations, which relate features such as metabolic rate to body to size [91]. Using the observation that cells and organisms are constrained in their growth by resource distribution networks, predictive models can be generated that accurately provide values for the scaling exponents observed in a number of diverse biological systems. Scaling relations, due to their ability to 'predict' the values of system parameters based on other measured quantities, represent perhaps the closest approach so far to a predictive theoretical biology, akin to theoretical physics (note: here prediction pertains to macro-level properties of networks and not their precise microphysical instantiation).

Although the appearance of similar scaling laws in such diverse systems may seem coincidental, it may also point to deep underlying structural similarities. For example, abstracted to the level of interaction networks, cities resemble cells in their highly organized complexity. The material infrastructure of cities, ranging from the surface area of roads and the distribution of electric cables to the number of gas stations, has been shown to have scaling exponents $\beta < 1$ (see [86]), similar to the allometric scaling relationships observed in the material structures of biological organisms. Remarkably, this scaling behavior appears to be a universal feature of cities, and not just modern ones, but also ancient cities such as those in the pre-Hispanic Basin of Mexico [92].

6.1. Informational scaling

The foregoing scaling relations are based on the physical or causal structure of a particular network (its structure in terms of interactions among its material substrates). Intriguingly, the informational degrees of freedom in cities, such as wages, patents, and employment rates, seem to obey a very different scaling regime than the material ones, in general exhibiting scaling exponents $\beta > 1$ (see [86]). Thus, scaling in the material or physical structure of cities appears to differ significantly from that of the informational structure for the same physical system, with interesting implications for the mapping between the two. The scaling of non-coding RNA transcripts in eukaryotic cells, which play an important role in information processing within the cell, also display similar super-linear scaling [93] which differs from the sub-linear scaling observed in metabolism, noted above. This offers a further hint of interesting interactions between these two levels—*matter and information*—not just in cells and organisms, but in ecosystems and in social organization such as cities. If that is correct, then it could represent a universal signature of living systems and their artifacts.

In this paper we have stressed how informational patterning may exist alongside patterns in the 'hardware' or 'wiring diagram', yet not necessarily track it. Does this quasi-autonomy of information patterning extend to scaling laws? And if so, is there a systematic relationship between the hardware and software scaling exponents?

To explore these questions, we have used the concept of transfer entropy to illustrate how the information-matter duality might feed into the causal narratives in bio-systems. In the example of the fission yeast cell cycle network shown in figure 2, about a quarter of the node pairs are causally linked (joined by edges) and so display some *causal* flow (e.g. as quantified in [44] via that channel). Other pairs of nodes are not linked and therefore have no causal flow. However, the distribution of information transfer (measured by the transfer entropy) does not merely reflect the causal linkages in this system. Table 3 shows the results of our previous work on this network. Although the majority of node pairs are not directly linked they still have appreciable information transfer. In fact, over 40% of node pairs with no direct linkage nevertheless systematically transfer some information between them (correlation without causation). Conversely, 7.4% of nodes have an edge yet exhibit *no* information transfer (causation without correlation). We showed something similar in the three-node network in figure 1 discussed earlier, where no information transfer occurred from $a \rightarrow b$.

What are we to make of these results, assuming they are generic? Evidently biological networks controlling the cell cycle have evolved long-range correlations in their information processing organization, providing a biological example of collective behavior familiar from physics and engineering, in phenomena such as entrainment. It is intriguing to conjecture that if the dynamics of biological systems are re-cast in terms of information (software) they may more closely resemble the dynamics of non-linear complex physical systems. The fission yeast cell cycle network may then be regarded as a sort of 'hydrogen atom' of biology to illustrate other features of the causal and informational structure of biological networks, as we proposed in [81].

One such feature concerns the question of scaling laws raised in the previous section. We wish to know whether the network displays *scaling in information processing,* as captured by transfer entropy. To assess features that may be unique to biological organization, the results can be compared to random network ensembles. This was reported by us in [81], where the scaling of information processing in both fission and budding yeast cell cycle Boolean network models was compared with large ensembles of two classes of random networks: Scale-Free (SF) and Erdös-Rényi (ER). The ER networks were constructed by fully randomizing the inhibition and activation edges, relative to the functional fission yeast cell cycle network. The SF networks were constructed by similarly randomizing the edges, but subject to the constraint that each node retain the same number of inhibition and activation links. The ensemble of ER networks are therefore homogeneous, with respect to the distribution of edges among nodes (i.e. on average there are no hubs). By contrast, the SF networks are constructed so as to share important topological features with the comparison biological networks—such as a common degree distribution, which ranks the number of edges per node. For the cell cycle network this distribution is heterogeneous due to the presence of hubs in the network. While the cell cycle network is too small to exhibit scale free topology with just ten nodes, for larger biological or other complex networks that are scale-free this algorithmic procedure would generate scale-free randomized network ensembles.

Table 2. The hallmarks of life.

Hallmarks of life
Global organization
Information as a causal agency
Top-down causation
Analogue and digital information processing
Laws and states co-evolve
Logical structure of a universal constructor
Dual hardware and software roles of genetic material
Non-trivial replication
Physical separation of instructions (algorithms) from the mechanism that implements them

Note: Adapted from Walker and Davies [8].

Table 3. The distribution of transfer entropy (TE) between pairs of nodes in fission yeast cell cycle networks, classified by pairs of nodes that are correlated (TE > 0) or not (TE $= 0$) and causally interacting (edge) or not (no edge).

	Edge	No edge
TE > 0	23.46%	43.21%
TE $= 0$	7.41%	25.93%

Note: The values indicate the ratio of the number of node pairs in each category to the total number of node pairs for each cell-cycle network. Table from data presented in [81].

The results of comparing information processing in the biological network and random network ensembles reveal statistically significant differences in the distribution of information processing that distinguish the biological network from random (see figure 3). Intriguingly, in the 'vital' regime where the difference is most pronounced, the distribution of information processing is dominated by information transfer between pairs of nodes that are *not* directly causally interacting (that is, it arises due to the collective properties of the network).

The results shown in figure 3 do indeed support the idea that biological networks possess additional 'hidden' scaling laws in information-processing, and it is tempting to suppose such laws will turn out to be a universal signature of biological organization since they are specifically associated with biological *function*. We described briefly in section 5.1 the presence of a 'control kernel' for the yeast cell cycle network [81], this being a small subset of nodes (highlighted in red in figure 2) that regulate the global function of the network by canalizing the states toward the primary attractor (this being the biologically functional resting state of the cell). The biologically distinct regime of the scaling relation in figure 3 is dominated by information transfer to and from the control kernel nodes.

Control kernels have been discovered in a number of gene regulatory network models, and have interesting information-theoretic properties themselves. In particular, the control kernel nodes as a set take on a distinct value in each of a network's attractor states, and thus the set is related to the *distinguishability* of these states and perhaps even to a coarse-graining of the network's state-space that may be directly relevant to biological function [81]. The control kernel nodes also play the dominant role in information storage in the network.

7. Hidden simplicity in evolution

As we have remarked, despite the daunting complexity of the physical world, physicists pin their hopes on the existence of simple underlying laws and principles. An object like the sun, for example, is undeniably complex in many of its details, but almost all aspects of solar physics can be traced back to the relatively simple laws of gravitation, nuclear and particle physics, thermodynamics, magnetohydrodynamics, radiation transport theory, etc. Even in complex systems such as turbulent flow or deterministic chaos simple mathematical laws or rules generate extraordinary complexity.

There is a widespread assumption that the universe as a whole, and Earth's biosphere in particular, are on a trend to ever-greater complexity [94]. It is of course obvious that the biosphere in general, and some organisms in particular, are more complex today (in some sense) than one million years after microbial life started (see, for example [95]). The key question, however, is whether there exists a hidden 'principle of complexification' in biology, systematically driving organisms to evolve more complex forms and driving the biosphere as a whole to a richer web of life, or whether the appearance of a trend is merely due to a selection effect—that humans, as a product of complexity, look back and trace the complexifying lineages that lead up to our species while ignoring other species that have become simpler [96] (such that our vantage point is 'post-selected'). Often this alleged complexification trend is extended to the origin of life too; many prominent scientists today claim that the universe is teeming with life on the basis that suitable chemical mixtures will almost inevitably complexify to life given enough time. The Nobel prize-winning biologist, Christian de Duve, referred to this trend by claiming that 'life is a cosmic imperative' [97]. Among the SETI community, the trend is often extended from the origin of life to the evolution of intelligence, leading to the popular view that we are not alone in the universe and that even our own galaxy may possess a large number of intelligent species and even technological civilizations, despite no direct evidence that this is in fact the case [98].

Complexification trends are familiar in many branches of science and engineering, such as condensed matter physics, fluid mechanics and non-equilibrium chemistry. One such trend is the phenomenon of self-organization, a major field of research in its own right. Some nonlinear systems, when driven far from thermodynamic equilibrium, may reach critical 'bifurcation points' at which the system leaps into a new state of organized complexity. A familiar example from physics is the Bénard instability in fluids, and a familiar example from chemistry is the Belousov–Zhabatinski reaction (see, for example [99]). So, perhaps there is some basis for a generalized 'life principle' or principle of advancing biological complexity all the way from chemical soups to intelligence? Unfortunately, in spite of the popularity of the idea, no such principle has been discovered or demonstrated, so if it exists, it remains well hidden. Moreover, the very concept has attracted some fierce criticism. Gould for example [96] has argued strongly that evolution has no intrinsic directionality. Darwin's notion of the tree of life, claims Gould, gives the false

notion of progress in evolution (e.g. to ever greater complexity); Gould suggests the tree of life should be replaced by the metaphor of a bush. And certainly there are many examples of organisms becoming simpler over time, presumably because complexity carries metabolic and other costs. Any impression of progress, he says, stems from confusing mere diffusion into the space of possibilities with an organized trend. Given that life started out simple, then random changes will very likely produce greater complexity at the outset, and the tail of the complexity distribution will tend to grow over time as more and more complexity outliers evolve. But this is not a principle of complexification so much as simple statistics. Gould suggested that the widespread tendency to see biology in progressivist terms is a hangover from an ancient teleological view of the world with its religious underpinnings. Certainly at the time Darwin published his theory of evolution, progressivist philosophy (applied mostly to social systems) was popular. Nevertheless, if there exists hidden 'simplicity in complexity' lurking in biology (or even in cosmology) it would represent a huge advance in our understanding to elucidate it. To investigate this topic, some simple toy models can be examined for complexification trends to determine what general mathematical or informational prerequisites may be discovered.

7.1. Pathways to complexity

In the examples we reviewed in section 6, complex states arise from the repeated application of a simple, fixed mathematical rule. But the essence of life is evolution and change, even in its underlying dynamical principles. It is a contrast with physics keenly appreciated by Darwin and eloquently expressed in the closing passage of his book *On the Origin of Species*:

> *"whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved"*. [100]

Since at least the time of Newton, physics has been founded on a fundamental asymmetry between *laws* and *states*. On the one hand, physical states are generally time-dependent and contingent, whereas the laws of physics are regarded as timeless, immutable and universal. So while the world evolves, the laws themselves are supposed to remain fixed, even in conditions as extreme as total gravitational collapse. Although the immutability of the laws of physics is occasionally challenged [101–103] it remains the default assumption among the vast majority of theoretical physicists.

The asymmetry assumption at the heart of physics has been imported into all other disciplines in which dynamics plays a role, including economics. In many specific biological processes, this assumption seems sound: for example, when modeling predator-prey dynamics. But in a more general sense, it fails. The problem stems from the dearth of any known quasi-universal biological laws of the character of the laws of physics. Different biological processes obey different rules, and because organisms and their internal components are frequently changing, the rules may change with them. This is in fact the essence of epigenetics. In the development of multi-celled organisms, a single cell divides and differentiates into a variety of cell types with very different properties. In the human body, for example, liver cells, skin cells, fat cells, blood cells and lung cells fulfill very different functions, and follow very different rules. Yet all have identical DNA. What differentiates these cell types is differential gene expression that changes over time. Thus the 'activity state' of DNA—how many and which genes are expressed—determines many of the cell's properties. If gene expression changes (for example, during development, or in cancer) the cell may switch to a dramatically different trajectory.

7.2. State-dependent dynamics

In light of the foregoing, a more realistic model of biology should incorporate the possibility that the rules themselves change during the complexification process [8, 57]. This can be achieved in two ways: by making the rules time-dependent according to some fixed-in-advance meta-rule, or allowing the rules to be determined by the *state* of the system: as the system evolves, so do the rules that govern it [60, 61, 104, 105]. The latter concept comes closer to real biology, because it incorporates two of the hallmarks of life: self-reference and top-down causation.

Very little attention has been given to the theoretical development of state-dependent dynamics as a novel way to generate complexity from simplicity, partly because of its unfamiliar nature, but also because of mathematical difficulties. An example where self-referential dynamics are explicitly studied is provided by Kaneko and colleagues in *functional dynamics,* which considers discrete maps of self-referential functions [60, 61]. The dynamics of such maps is highly novel. For example, they emulate the evolution of natural language, where the self-referential feedback acts as a filter that produces a corpus of words that are each a fixed point of the dynamical model.

We recently demonstrated similar dynamics in cellular-automata (CA) models with state-dependent rules [104, 105]. A simple 1D CA is a linear array of cells, each of which can be either empty (0) or filled (1) [106]. An example is elementary cellular automata (ECA) that are 1D, with a rule that depends only on nearest-neighbor interactions for updating the states of individual cells. For an ECA, the state of the array advances in discrete time steps according to one of 256 possible rules that consider the instantaneous state of each cell plus that of its two immediately adjacent neighbors. In the conventional treatment, an initial state is chosen and the state of the array is advanced stepwise for as many time steps as are of interest according to the fixed rule. To adapt this system to incorporate state-dependent dynamics, the rules themselves as well as the cells are continually updated using an algorithm or map that assigns a rule to each step based on the overall (global) state of the ECA at the immediately prior step. For example, a twenty-four cell ECA studied by Pavlic *et al* takes the instantaneous state of the array and uses coarse-graining to generate a number that is in turn used to select an update rule drawn from the 256 rule set, via a lookup table [104]. With the right initial conditions, some look-up algorithms can produce

intricate patterns over many generations. These types of self-referential ECAs can generate rich heterogeneity and diversity within a single evolving ECA, and represent a novel pathway to complexity that remains largely unexplored on account of its high degree of nonlinearity and computationally demanding complexity.

Although self-referential ECAs model (albeit crudely) one important hallmark of life (state-dependent dynamics), merely mapping the state into the rule set suffers from an obvious and severe limitation: these generalized ECAs are still finite-state closed deterministic systems, so there will always be a state of maximum complexity, however complexity is defined. A more powerful ECA model would permit unbounded, or open-ended, complexity. The property of open-endedness is critical to life and its origin, because if an evolving system gets hung up at a local complexity maximum, further evolutionary advance is impossible. To attain open-endedness, the system cannot be causally closed—it must be open to a (normally changing) environment. The property of open-endedness in ECAs has been investigated by us in [105] where we model the openness feature by allowing a state-dependent ECA, designated as 'organism', to couple to a second ECA that plays the role of an external 'environment'. The environment itself evolves from a chosen initial state according to a *fixed* rule, whereas the organism rule evolves as a function of three variables: the current state of the organism (its 'phenotype'), the current rule ('genotype') and the current state of the environment. By incorporating the state of the environment in the assignment of the organism's update rule, the organism ECA is transformed into an open system. The evolving organism's rule is loosely analogous to an evolving genotype while its state corresponds to phenotype. Open-ended evolution can occur either in the genotype or phenotype and is formalized as a non-repeating pattern in either the trajectory of rules (genotype) or the trajectory of states (phenotype) within the Poincaré recurrence time of an equivalent isolated system. The dynamics remains constrained by the Poincaré recurrence time of the total system, which is, however, vastly longer than the recurrence time for an isolated ECA. But within that constraint, a handful of state-dependent ECAs are found to display non-repeating complex patterns over times much longer than the Poincaré time of an isolated ECA and can be driven toward states of higher complexity (longer non-repeating patterns) by coupling to larger environments. It remains unclear what is the key feature that singles out this handful, but time-dependent rules are a necessary pre-condition to permitting any such system to be part of this class.

7.3. Information as a selectable trait

The essence of Darwinian evolution by random variation and natural selection is that nature cannot look ahead and anticipate future needs, thereby shaping the evolutionary pathway towards better fitness. This places Darwinism in contradistinction to Lamarck's theory of evolution, in which it is postulated that organisms strive to improve their fitness and pass on to their progeny characteristics acquired in their lifetime. Darwinism removes from biology the vestige of teleology, an ancient notion of causation in which events in the world are directed to some final goal or purpose. Darwinian evolution is blind, purposeless exploration of the space of possibilities, in which the lucky variants are favored for survival at the time, leading to differential reproductive success of the fitter.

Our hypothesis of the duality of matter and information in biological systems raises a fascinating question. *Does natural selection operate on software as well as on hardware?* That is, is there a 'cyber-Mount Improbable' to climb alongside 'Mount Improbable?' [107] Expressed more formally, does the informational architecture of a living organism constitute a selectable trait in the same manner as its morphological and physiological architecture? The answer would seem to be yes [105], or how else has the software of life evolved to such a level of efficiency and complexity? Surely not as a fortuitous epiphenomenon? However, this conclusion immediately raises again the problem that has been a recurring theme in this review: what, precisely, is meant by 'biological information' as opposed to generic definitions of information?

One area where the concept of information has played a particularly prominent role is evolutionary theory. While for decades evolution has been discussed as a process that is at least in part describable as the accumulation of information over time, it is only very recently that information itself (specifically mutual information between genomes and environment) has been identified as potentially driving organismal fitness [108–110]. These studies are aimed at addressing the unresolved question of whether the accumulation of information in genomes is under direct selection as the driver of fitness, or if it is instead a passive side effect of increasing fitness. The results seem to indicate that information is indeed a selectable trait, particularly when organisms are subjected to time-varying environments. Recently information theory has even been used to define individuals [111] and may be essential to defining the hierarchical structure of living systems [112].

8. Conclusions

Most scientists acknowledge that life—both its origin and nature—remain deeply baffling. To a physicist, living systems seem almost miraculous in the way they harness physical and chemical processes to achieve states that would be inaccessible to inanimate systems [113]. Biological organisms display many remarkable properties, and although it is notoriously hard to pin down precisely what marks out living matter as distinct, the role of information offers the most promising way to organize our thinking about them. In this review we have addressed an open question: *do there exist deep and perhaps universal principles in biology, masked from us by the bewildering complexity of life, but possibly accessible to inquiry by focusing on the abstract informational aspect*?

It is clear that new concepts of complexity may be necessary to explain life, which could lie outside the scope of current approaches to information theory (see, e.g. [114]). We have stressed the analogy between living systems and electronic and computer systems, which can be understood in terms of

logical functions and modularized information circuits without reference to the detailed molecular processes going on inside the components, and conjectured that great simplifications in biology may arise from focusing on information management and logical function in cells and organisms too, using both current methods of information theory and speculating on new conceptual frameworks that may be necessary to make further progress. These ideas were illustrated by applying information theory to some idealized biological systems, such as the genes that regulate the cell cycle of yeast, showing how such an analysis can uncover hitherto hidden but striking mathematical patterns within the abstract informational realm. We have conjectured that certain informational motifs may be universal. Indeed, we think it may be possible to characterize and classify life via its informational taxonomy and that this scheme may even apply to extraterrestrial life, representing a law-like framework for universal biology akin to that employed in theoretical physics.

We have also explained how very simplified cartoon dynamical systems like cellular automata may be adapted and used as a theoretical test-bed for ideas about information flow and management. Although such models are computationally demanding, they may be used to identify novel pathways to complexity, for example, via state-dependent dynamics. This aspect of dynamical systems theory remains in its infancy, but is likely to find many applications to biology, as well as the transition from non-life to life.

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