Life is the self-regulating conversion of thermodynamic disequilibria into directed motion

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Abstract

A range of philosophical difficulties surround the attempt to produce a theory and definition of life. However, many traditional arguments against the attempt are no longer valid or overlook the fundamental problem: the human difficulty of understanding and integrating knowledge across a range of disciplines and scales, from the physics of atoms and molecules to the networks of evidently ‘working’ matter comprising structures such as cells. Recent empirical evidence shows that a range of biological molecules, including ribozymes and enzymes with rotating or ratcheting subunits, undergo repetitive conformation state changes driven by thermal agitation and energy exchanges, in turn governing catalysis of reactions fundamental to metabolism and replication. These molecules exhibit disparate structures but share the principle of repetitive unidirectional conformation changes driven by thermodynamic gradients, producing directional motion. Here, life is defined as a self-regulating process whereby matter undergoes cyclic, unidirectional conformation state changes that convert thermal agitation and excitation into directed motion, performing work that locally reduces entropy. By extension, a living thing is a structure comprising, at least in part, an autonomous network of units operating on the heat engine principle. Non-living structures do not perform work via integrated heat engines, with atoms and molecules that dissipate heat randomly. Death is the loss of integrated heat-engine function in a material structure (cell, tissue, organ or individual). The principle of self-regulating networks of heat engines is independent of any specific chemical environment or molecular structure; this definition should apply universally across biospheres characterized by differing biochemistries.

The biology and philosophy of the ‘life’ dilemma

Distinguishing ‘living’ from ‘non-living’ structures implies the existence of a single distinctive property, but life is typically described with a combination of properties (e.g. growth, structure, self-sustaining replication, capacity to evolve, homeostasis and metabolism) to the extent that ‘biologists now accept a laundry list of features characteristic of life rather than a unified account’ (Mariscal and Doolittle 2018). Indeed, many of these features are not unique to biological organisms, also exhibited by putatively non-living systems such as crystals, fire, and cyclones. The literature dealing with theories of life and the problems inherent to defining the phenomenon is vast and has a long history (see Mariscal and Doolittle 2018), and a broadly accepted definition has proven so elusive that even the attempt to define life is now deeply controversial (e.g. Machery 2012).

Here I start from the most prevalent contemporary examples of ‘life definition problems’ to illustrate these philosophical difficulties but, more optimistically, I demonstrate why these arguments are either irrelevant or no longer an obstacle. I then use recent discoveries to formulate a robust theory and definition of life.

A modern classic argument against the prospect of a scientific theory of life arises from the fact that all organisms on Earth have a common evolutionary origin. Thus, we can only observe a single type of life (n=1 sample), which could even be atypical of life in the universe (Sagan 1974). We could respond to this apparent dilemma with workaround solutions, such as treating life on Earth as a separate entity (even literally as a single living entity; Mariscal and Doolittle 2018). However, this is beside the point; scientific theories are possible explanations, supported by testable hypotheses which are accepted or rejected by observation and experiment. In other words, a scientific theory can exist so long as it has minimal empirical support, and is either refined or superseded as further hypotheses are tested. Theories have small beginnings and expand into the unknown. We have an excellent precedent that n=1 is not a serious impediment to general theories of how living things operate. When Darwin and Wallace (1858) presented their theory of
evolution by means of natural selection, observational and experimental evidence was strong (bolstered by Darwin’s (1859) extended thesis). Over the following decades, especially with the discovery of the structure of nucleic acids (Watson and Crick 1953), with the fine details of evolutionary relationships and events revealed by genetic studies (e.g. Givnish et al. 2014; Suh et al. 2015) and physical evidence of numerous transitional forms in the fossil record (e.g. Hou et al. 1999; Clarke 2004; Daeschler et al. 2006), a range of hypotheses have been tested and have increased our confidence in the theory to the point that most biologists agree that it is extremely probable (not a fact or absolute truth, *per se*). It provides a powerful explanation of how different types of organisms can exist, even though we can study living systems only on one planet. If we find cells on Mars or Europa (≥1) the theory could help predict how groups of these entities evolve, but they could evolve using a different principle to those on Earth (we cannot know without testing hypotheses). Crucially, even if we find organisms on a thousand planets it would not change the theory of natural selection; it would change the degree of confidence we have in it. We are free to suggest a theory of ‘life’ based on a single biosphere, and within that biosphere can test a range of hypotheses to determine whether or not they agree with the theory. Scientific discovery beyond Earth may never happen, but is not a prerequisite.

A much different ‘life definition problem’ proposes that definitions of even simple words such as ‘dog’ are plagued by exceptions and ambiguities (Machery 2012). Although a layperson would intuitively recognize a dog, it would be impossible to define ‘dog’ unequivocally in a way that thoroughly prevents non-dog entities being described by the word. However, biology has a precise method for defining ‘dog’, based on descriptive taxonomy (Latin names associated with specific phenotypic characteristics) and evolutionary hypotheses that are evident from the sequence and comparison of mammal genomes. A ‘dog’ is; a mammal (Mammalia; animals exhibiting hair or fur, milk secretion in females and, typically, live birth), Carnivora (a predominantly flesh diet), Canidae (teeth with adaptations for processing meat, upright pinnae, bushy tails, long muzzles relative to head length; Miwari 1890), *Canis* (characteristic size and shape of particular teeth and relative breadth of the palate), and *C. lupus familiaris* (domesticated, exhibiting specific genomic cytochrome B sequences, as detailed by Aagnarsson et al. 2010). This phrase, although longwinded and reliant on external definitions, is a definition that conforms to the definition, and it can be used to examine an entity and state ‘this is [or is not] a dog’ with a high degree of confidence. The key lies in using a system based on unambiguous, quantifiable criteria, and synthesis of high-quality scientific information.

Clearly, understanding scientific definitions requires training and technical knowledge; for ‘dog’, training in dentition and genetics. Machery (2012) argues that because scientific definitions are more technically complex and precise, they can never be the same as folk definitions, and the word ‘life’ will always have different meanings for scientific and lay audiences; *ergo* it is impossible to produce a universally accepted definition. This is true, in the sense that despite the weight of empirical evidence, not everyone accepts the theory that planet Earth is a spheroid (see Landrum et al. 2021). However, the aim of philosophy and science is not to satisfy everyone’s worldview, but to provide insight. Defining the word is not the point of the exercise: the attempt is to delineate the phenomenon. Words and definitions are tools in this attempt. It would be absurd to reject the theory of evolution by means of natural selection because the word ‘evolution’ is synonymous with ‘development’ in lay terminology and means different things to different people.

Another contention is that definitions of life have been formulated very differently across a range of scientific disciplines, including different fields of the natural sciences and artificial life (Alife) research (Machery 2012). In fields such as astrobiology there may be various definitions for various applications (not all of which attempt to explain life). A working definition may be satisfactory for practical applications such as detecting habitable environments, whereas attempts to understand the origin of life are based on precisely the same kind of reductive biological sciences used to scrutinize the life presently occupying the Earth, and definitions have similar theoretical goals. Definitions for Alife can only be speculative until biology has successfully explained organic life, from which to draw comparisons. This is not to say that only biology matters, rather that a realistic theory of life in organic systems would be a useful starting point for speculative considerations of life (as I show below, this is indeed the case). In a sense, biology currently fails in its duty to inform other branches of science, and a lack of a clear definition of the phenomenon at the heart of biology is a major source of embarrassment.

Essentially there is good reason to attempt a theory and definition of life, and no good reason not to. An initial aim of the current article is to show that science has now achieved a sufficiently detailed understanding to allow a robust theory and definition of life. A spectrum of complexity is evident from simple chemical compounds, complex macromolecules, cells, multicellular microbes through to large-scale organisms, and the point along this spectrum at which chemistry becomes biology (abiogenesis) is difficult to identify and define, lying at the empirical and philosophical heart of the problem (Pross 2016). However, organisms, as material objects, consist of atoms and molecules and thus exhibit measurable physicochemical properties, and at every point along the spectrum scaling from atoms to organisms we now possess the methods to quantify and compare the states of matter, and have actually done so. Indeed, we can directly visualize in real time the movements of individual molecules (e.g. Kodera et al. 2013) and discern the difference between animate and non-animate matter. This simple fact suggests that it is reasonable to expect that a distinguishing physical property may be detectable – a property inherent to the matter comprising organisms, yet not evident for non-biological matter – and that we can satisfy the requirement for a system and testable theory of life from which the definition of a single process emerges.

The crux of the problem lies in detecting a single process common to a vast array of disparate biological structures. The real barrier to doing this, demonstrated by the failure of folk definitions of life, is the requirement for integrating specialist knowledge across a broad range of scientific disciplines, encompassing various scales of investigation. This is a human limitation, reflecting more on human nature than it does on biological processes, and it is a limitation that can be overcome. Recent evidence from a range of unrelated experimental studies is revealing a single shared characteristic of certain biomolecules, which is not due to the structure of these molecules *per se*, but the common physical principle by which they operate. Intriguingly, it may be that we have already detected a single property of matter that can explain the state of ‘being alive’, but we are only starting to recognize just how pervasive this property is throughout biological systems and, indeed, defines them.

**Long-term vs. immediate life processes**

In Biology, the immediate state of organisms must be considered in the context of long-term processes such as heredity and natural selection, which often take center stage in the consideration of the origin, operation and definition of life (Dawkins 2004). Indeed, a recent definition of life as ‘a self-sustaining kinetically stable network derived from the replication reaction’ (Pross 2016) acknowledges the importance of longer-term events such as replication. It also successfully consolidates many evident features of life: replication and metabolism appear to have arisen together in networks of RNA (or functionally similar) molecules catalyzing reactions for one another; life actively
maintains stability by dynamic kinetic means rather than chemical inertness; molecules are variable and thus subject to natural selection, with a gradient of increasing complexity and functional effectiveness through time linking simple chemistry to the systems chemistry of living entities (Pross 2016).

However, reliance on long-term processes such as evolution to define and recognize life is problematic for several reasons. We may be able to demonstrate that cells in a sample grow, multiply, produce further generations and evolve. But what if the cells are not amenable to culture? What if we cannot observe them replicating or evolving? Difficulties such as these masked the existence of an entire biological domain, the Archaea, which was only determined as recently as 1977 from DNA fragments in environmental samples (Woese and Fox 1977). The widespread distribution and importance of this domain of life throughout a range of marine and terrestrial ecosystems has only recently become appreciated (e.g., Olsen 1994; Robertson et al. 2005).

Additionally, life can be interpreted as an instantaneous state or short-term process, occurring moment-by-moment rather than over the timescales of generations. A mule, incapable of reproduction and of participating in evolution, is nonetheless capable of working, eating and breeding. It is considered to be alive in an instantaneous sense. To understand what ‘alive’ actually means, we must be able to recognize an immediate distinguishing property characterizing the state of being alive. What is this property?

This was partially answered by Erwin Schrödinger (1944) when he recognized that life is characterized by the spontaneous creation of order in a universe characterized by increasing disorder, coining the term ‘negative entropy’. He also suggested that instructions controlling this process may be encoded in ‘aperiodic crystals’ or molecular matrices with irregular repetition of atoms encoding information, and that in some way this process may involve the chromosomes. We now know that DNA is a flexible polymer, not a rigid crystal, but Schrödinger’s view nonetheless suggests that life is fundamentally a process by which structure is created from the aggregation and organization of matter and energy according to information encoded in aperiodic molecules. This almost constitutes a definition of life, but lacks an explicit mechanism.

It is clear that the single property defining life must somehow involve the mechanism of local entropy reduction, and that this is governed by biological molecules. However, a wide range of different types of biological molecules are clearly active in entropy reduction, and it is not immediately evident that a single property shared by these molecules underpins their ability to aggregate and organize matter. It is evident, however, that some fundamental properties are shared across a range of molecules, principally involving how they respond to the thermal environment and how they change conformation under excitation.

Random vs. directed motion

Motion is a fundamental property of matter. Atoms and molecules constantly vibrate and the extent to which they do so, by definition, determines the temperature of a system (atoms move even at absolute zero, due to the underlying fluctuations of zero-point energy; Sciana 1991). Furthermore, thermal agitation (heat) can be exchanged by physical contact (conduction) or radiation, and atoms and molecules can become additionally ‘excited’ beyond their stable ground state, for example by photon excitation. Excitation represents the temporary jump of an electron to a higher orbital and an increase in atomic radius, and thus the size of the atom. As atomic radii change, so do the dimensions of molecules, resulting in additional molecular motions, which relax with the decay of the excited state when a photon is emitted. All these extremely rapid atomic and molecular-scale motions are crucial to physical and chemical processes. For instance, thermal agitation and the ‘molecular storm’ of bombardments amongst molecules results in Brownian motion (the random motion of particles as observed in suspension) and ultimately underpins phenomena such as diffusion. Excitation of pigment molecules is fundamental to processes such as photosynthesis: the ‘head’ (porphyrin ring) of the chlorophyll molecule swivels when excited by a photon, bringing it closer to other chlorophylls and allowing the excitation state to be transferred (Furuichi et al. 2000).

Indeed, while thermal agitation and excitation induce haphazard motions and conformation state changes in most molecules, some molecules exhibit motions that are constrained by their shape and the interactions between their component atoms: sub-units are free to flex or rotate in only one plane. In other words, molecules exhibit an inherent range of possible conformations that are ‘sampled through motions with a topologically preferred directionality’ that are constrained by the properties of the molecule itself (Grant et al. 2010). Thus, thermal agitation and excitation can induce directional motions in certain molecules, the character of which is inherent to the structure of these molecules. In fact, this is particularly evident for biological molecules.

For example, the active domains of motor proteins can flex in specific directions, but not others (Grant et al. 2010; Astumian 2000; Astumian and Hänggi 2002; Kodera et al. 2010), the spinning sub-units of enzymes such as ATP synthase or V-ATPase spin in one plane (Walker 1997; Weber 2006) to generate mechanical ‘torque’ that performs work (Uchihashi et al. 2011), catalytic RNA molecules (ribozymes) shift between conformation states (Takagi et al. 2002; Lilley 2011), the ribozyme components of ribosomes ratchet along mRNA to provide the driving force of protein synthesis (Ratje et al. 2010; Spinr and Finkelstein 2011), and RNA polymerase similarly ratchets along the DNA molecule during transcription (Hoffmann 2012). Indeed, enzymes (catalysts) exhibit conformational state changes, and the resulting physical motion is necessary to catalyze reaction (as it facilitates substrate binding (Narayan et al. 2016). Many non-motor enzymes are known to essentially produce ‘directional mechanical force’ (Zhao et al. 2018) or ‘convert chemical energy into mechanical force’ (Oster and Wang 2000) to perform work: directional motion, torque generation and power output are thought to be general properties of asymmetric proteins (Stinchower and Gilson 2018), Thus, across a broad range of biological macromolecules, flexibility and asymmetry results in consistent, cyclic, and directed mechanical motion that can dependably perform work.

While the motion of molecules is typically inferred from structural relationships and computer modeling, we can now directly observe molecular movement. High speed atomic force microscopy has demonstrated the conformational motions of the myosin V motor protein, driving overall movement of the molecule along actin filament tracks as part of the mechanism changing the elongation of muscle fiber cells (Kodera et al. 2010). The myosin V molecule ‘walks’ hand-over-hand along the actin filament in what the authors describe as a ‘unidirectional processive motion’, generated by a combination of thermal excitation followed by the interaction of adenosine triphosphate (ATP) with ‘head’ domains to temporarily fix them in position. These head domains change conformation in a very specific manner. Each domain can flex, but only in a single plane and to a very specific degree, described as a ‘rigid hinge’ motion (Kodera et al. 2010). The extent and direction of motion are not dependent on the surrounding context, such as interaction with the actin filament, but by the arrangement of atoms in the molecule and the conformational state of the head domain: slight deviation in bending would result in attachment to actin subunits at incorrect distances or directions, or in attachment to neighboring actin filaments, any of which would result in a disastrous lack of function, and the extent of conformational change is an inherent property of the molecule (Kodera et al. 2010). The principal function of these motions is to generate mechanical force, which can
be measured at the macro scale as the force with which the muscle contracts, leaving no doubt that these molecular motions perform work.

Ribozymes, consisting of RNA, are structurally very different to motor proteins, but can nonetheless function in a similar way as enzyme-like catalysts governing a diverse range of reactions (Horning and Joyce 2016). Artificially designed ribozymes can even perform ‘riboPCR’ (i.e., copy RNA templates in a manner similar to the polymerase chain reaction, PCR; Horning and Joyce 2016). This range of metabolic and replicative activities is thought to be a prerequisite for abiogenesis (Johnson et al. 2001; Joyce 2009). Like motor proteins, ribozymes also perform these activities via directional motion. For example, the Tetrahymena ribozyme includes a mobile motif (the ‘P5abc three-helix junction’) which can reversibly shift between two extreme conformation states: ‘extended’ and ‘native’. Although it moves through a range of subtle intermediate states to achieve these endpoints the process essentially involves two principal conformation step changes, occurring rapidly over a period of 10 and 300 ms, respectively (Piumbridge et al. 2018). Thus, ribozyme function depends on a single property: the ability to reliably switch between conformation states. Just as the motion of motor proteins and other enzymes produces directional mechanical force, it is conceivable that ribozyme motions also generate and apply directional force during catalysis, although this has yet to be measured.

It is clear from these observations that Schrödinger’s negative entropy is created via unidirectional conformation state changes under thermal agitation, essentially converting random agitation into directed motion and thus work.

**Life is an uphill struggle**

The real biological molecules presented above can all be considered, theoretically, as ‘Brownian ratchets’ (Hoffmann 2012) or ‘Feynman–Smoluchowski ratchets’ (Moore 2019): i.e., systems for converting stochasticity into order. Thermally agitated systems may include components that are free to move in one direction, but not backwards, effectively converting random movements into directional motion, akin to a ratchet comprised of a rotating gear stopped by a spring-loaded pawl, driven by an agitated paddle wheel. At first glance this may seem to represent an impossible perpetual motion machine, whereby background thermal agitation is inevitably converted into continuous progressive movement (it was originally proposed as a thought experiment; von Smoluchowski 1912). Indeed, when there is an even temp–erature across the mechanism the agitated pawl jumps and slips, and the gear has an equal probability of forward or backward rotation. However, Richard Feynman (Feynman et al. 1963) suggested that the probability of the gear moving in one particular direction increases if the pawl is at a lower energy state (less agitated) than the paddle wheel, i.e., with a net ‘energy input’ to the system or, more correctly, with a thermodynamic gradient or disequilibrium across the system (see also Moore 2019). As such a mechanism essentially relies on a temperature differential to perform work, Feynman et al. (1963) referred to it simply as a ‘heat engine’. We know that this is possible: as a proof of principle, a physical ratcheting mechanism has been constructed that converts inputs of non-directional fluctuating forces such as white noise into unidirectional rotation (i.e., a device that spins in a noisy environment; Norden et al. 2002).

Despite reducing entropy locally, heat engines do not contradict the second law of thermodynamics (that entropy in a system always increases), because the work they perform represents a relatively small decrease in entropy connected to and driven by a larger entropy increase: i.e., a localized decrease but a net increase. The driving disequilibrium across the mechanism can be thought of as an ‘environmental’ (positive entropy) disequilibrium, but the ratchet portion essentially creates a further weak disequilibrium by performing work (negative entropy). In simple analogy, a torrent flowing across a waterwheel operates a pulley system to lift a bucket of water uphill: a small quantity of water can move against gravity only because a much larger quantity moves with gravity. More precisely, heat engine mechanisms are akin to the escapement of a clock, in which the kinetic energy of a rotating gear is alternately restrained by, then pushes, an oscillating pendulum (Branscomb et al. 2017). A simple force is regulated to produce a precise movement, and the entire mechanism can only work with the simultaneous interleaving of both input and output actions (Jencks 1989; Branscomb et al. 2017). The ‘downhill’ (toward thermodynamic equilibrium) gradient is both regulated by and drives the ‘uphill’ (entropy reducing) gradient. Living systems are uphill systems, but can only exist in a downhill environment, necessarily exploiting thermodynamic gradients and a net entropy increase (Branscomb et al. 2017).

What, then, of the role of chemical energy, or ‘energy carrier’ molecules such as ATP? Crucially, while thermal agitation is the ‘heat engine’ that induces motion (Hänggi et al. 1990), ATP acts essentially by fixing the motion of bio-molecules at a point far from thermodynamic equilibrium (i.e., ATP carries a disequilibrium; Jencks 1989; Jencks 1997; Astumian 2010; Branscomb et al. 2017). ATP is the tip of the ratchet that, via thermal ‘energy input’, stepping backward movement and favoring advancement, but thermal agitation provides the driving force. In other words, molecules such as ATP are ‘missing components’ of biological heat engines, required to temporarily complete the mechanism and thereby activate it, with the motion and work then resetting the configuration. While many of these concepts have previously been acknowledged as fundamental to life (Hänggi and Marchesoni 2008; Hoffmann 2012; Branscomb et al. 2017), the principle of unidirectional conformation state changes directing thermal agitation as the driving mechanism reducing local entropy has not been used to formulate an explicit theory or definition of life.

**The single property defining living systems**

The structurally diverse biological macromolecules discussed above exhibit a shared principle of operation: that of conformation state changes directing thermal agitation into unidirectional motion and thus work (the creation of negative entropy and structural motion by heat engines). Alternatively, molecules without preferred configuration state changes move randomly and dissipate energy inputs. This simple functional difference suggests the existence of two fundamental functional classes of matter, forming the basis of the difference between living and non-living systems. Thus life can be defined as a process:

*Life is a self-regulating process whereby matter undergoes cyclic, unidirectional conformation state changes that convert thermal agitation and excitation into directed motion, performing work that locally reduces entropy.*

Life is the self-regulating conversion of thermodynamic disequilibria into directed molecular motion. This process determines the immediate state of ‘being alive’, agrees with the concept of disequilibrium driving Feynman–Smoluchowski Brownian ratchets (Moore 2019; Branscomb et al. 2017), is a mechanism that aggregates matter to produce ‘negative entropy’ (Schrödinger 1944), underpins the ‘self-sustaining kinetically stable dynamic reaction net-work derived from the replication reaction’ (Pross 2016), its components are subject to the further long-term processes of mutation and natural selection (Darwin and Wallace 1858; Darwin 1859), and it is thus consistent with a range of fundamental biological and physical concepts. Lack of coordinated, directed motion in matter reflects a state of non-
life, and where directed motion was previously evident in a molecular network, this lack essentially determines death. ‘Animated matter’ really is an appropriate lay description for the essential process underpinning life, albeit one that does not quite capture the range of scales (nanoscopic and microscopic to macroscopic) involved.

Autonomy (Ruiz-Mirazo and Moreno 2012) and self-regulation via integrated networks (Pross 2016) are key concepts highlighted in this definition. Looms use cyclic conformation changes (mechanical action) to convert energy and matter (electricity and wool) into an ordered state (cloth) following a pattern encoded as a set of instructions (programmed information). However, looms are not self-regulating systems and require external input (from a biological organism) for their creation, maintenance, operation and programming. In other words, it is not the single ‘directed motion’ protein or ribosome (the single heat engine) that should be considered alive, but the integrated, self-regulating and self-replicating network of heat engines. If we wish to classify an object as alive or not, the definition is thus:

A living thing is a structure comprising, at least in part, an autonomous network of units operating on the heat engine principle.

Mules, dogs, humans, plants, bacteria all rely on networks of heat engines performing work and replicating within them. Organisms are ‘alive’ from one moment to the next due to the operation of heat engines. Within your cells, millions of heat engines continuously jiggles, bathed in thermal energy and activated by chemical energy, performing small tasks so numerous and rapid that the sum allows the operation of metabolism, physiology, movement, growth, reproduction, and all the macroscopic functions that we associate with life. As living beings, this is our defining physical interaction with the universe: the single distinctive property distinguishing ‘living’ from ‘non-living’ things.

Robustness in the face of the usual ‘special cases’

An objection to these definitions could be advanced if an exception to the rule is found (Machery 2012). Simple mechanisms, such as the device that spins in a noisy environment (Nordén et al. 2002) are not involved in networks that create structures, reduce entropy and drive evolution (they are not alive). ‘Classic’ exceptions to life definitions, such as fire, cyclones and crystals do not involve entropy reduction by heat engines (they are not exceptions; they are not alive). Fire is a self-sustaining reaction but increases entropy. Cyclones show structure due to convection and pressure gradients rather than work performed by heat engines. Diamonds, table salt and snowflakes exhibit growth, structure and entropy decrease during formation, but crystalization results from compaction at high temperature, precipitation from a solution, or by freezing of vapour, respectively, rather than being a product of heat engines.

Bacteria frozen in the permafrost or tardigrades frozen on Antarctic moss are alive, because metabolism (working on heat engine principles) does proceed, albeit extremely slowly, with cell components in a protected state known as cryptobiosis (e.g., Tsujimoto et al. 2016). Cryptobiosis, in which high concentrations of sugars and heat shock proteins are mobilized to physically support and thus protect biological molecules (including structures such as cell membranes, enzymes and DNA) is a widespread and well-studied phenomenon (reviewed by Clegg 2001). For example, plant embryos remain inactive but viable within seeds due to the ‘chaperone’ properties of sugars and proteins such as late embryogenesis abundant (LEA) proteins, heat- and cold-shock proteins; part of a universal cellular stress response that information changes (mechanical action) to convert heat engines (reviewed by Pierce et al. 2001). Most cells are capable of a degree of inactivity, crucial to survival of stress (sub-optimal metabolic performance imposed by variable or limiting environmental conditions; Grime & Pierce 2012).

Mature red blood cells, despite lacking genetic material, can be considered alive because they exhibit a network of enzymes that operate on heat engine principles (e.g. ATPases, ATPase-related flippases and flippases, carbonic anhydrase, etc.) to perform work. The cells die when the network ceases to function.

Prions (misfolded prion protein; PrP<sup>Sc</sup>) have biological origins and appear to replicate. However, they are structurally rigid (the conformation changes during their formation are akin to an irreversible collapse and crumpling; Lee and Chang 2019), and the ‘replication’ induced by PrP<sup>Sc</sup> has little to do with true replication (i.e., production of new complex structures from simpler materials following information inherited across generations); PrP<sup>Sc</sup> does not create, but alters the state of existing protein. Specifically, ‘cellular prion protein’ (PrP<sup>C</sup>; a nerve cell membrane transporter protein; Wulf et al. 2017) is altered in a way that happens to induce a cascade of further damage and conversion of PrP to PrP<sup>Sc</sup>. Furthermore, PrP<sup>Sc</sup> does not participate in a network that locally reduces entropy to create structure, but leads to tissue destruction and increasingly disordered states, increasing entropy. In other words, if prions are considered in the context of the above definition, they do not falsify it. They are not a ‘biological exception’ to the rule, they are simply not alive.

Neither do viruses represent an exception, but truly bridge the gap between life and non-life, because in their free state they are aggregates of molecules (a non-living state), but when they encounter cell membranes and are then intimately incorporated into metabolic machinery, they actively participate in the directed motion network (share the living state of the cell), which reduces entropy by converting simple resources into more complex copies of virus particles. Life is a process that can stop and start – chemistry becoming biology – should not be considered a single mystical event that happened just once billions of years ago; viruses perform their version of this trick every day.

Medical definitions of life and death are particularly interesting in the context of the above definitions, because they are directly compatible with them: although representing states and consequences occurring at the macroscopic scale, immediately evident to a qualified human observer. In the USA, the Uniform Determination of Death Act (UDDA) states that an individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. These are practical criteria that are intended to allow a legal definition of death. However, they reflect underlying biological processes, death being the moment when integration of heat engine networks ceases in (1) the heart or (2) the brain. Human bodies are a mosaic of life and non-life, meaning that medical death of the person (the entire organism) can be ascribed based on the irreversible failure of one organ (heart or brain) despite other organs being alive. In the case of live organ transplants, a living heart (with cells demonstrating active and integrated heat engines) removed from a donor with a dead brain (in which heat engine integration is quenched) is congruent with the definition of life, the medical state simply representing an evident representation of the underlying biological physical state. Certainly, medical and legal definitions of life or death do not represent scientific falsification of the above theory of life.

How could the above definitions be falsified? Brownian ratchets, or conceptual equivalents, are found in artificial systems such as liquid crystalline displays (Pal & Meyhöfer 2002), diodes (which impart unidirectionality on electrical current) or devices such as electronic switches that sort suspended particles (Germs et al. 2012), and a range of artificial nanoscale Brownian motion devices have been constructed (reviewed by Hänggi and Marchesoni 2008). These single systems do not build themselves. If an artificial network of devices were able to use a heat engine network
to reduce entropy, create order and thereby self-regulate, then it would not falsify the definition; it would be considered alive.

Other potential forms of life

Of the various forms of artificial life, based on hardware, software or artificial cells (‘hard’, ‘soft’ and ‘wet’ ALife, respectively; reviewed by Bedau 2003), digital software organisms seem the most far-removed from a definition of life based on matter. However, even computer software has a physical basis in the states (the presence or absence of charge and thus bits) of memory cells and the distribution of these states (physical addresses) across a memory chip. Complications exist, such as when states are represented indirectly in ‘virtual memory’ (distributed on the hard disc rather than arrayed on the memory chip), but the term entropy is used to represent the extent to which processes are physically distributed across hardware (e.g. Marco-Gisbert and Ripoll 2019). A virtual environment modelling unstructured systems such as a dust cloud will not only represent a high-entropy system, it will also literally exhibit higher entropy in the state of the memory chip in the real world. In comparison, a highly ordered virtual reality would exhibit relatively low entropy even in the real world, as a structured distribution of memory cell states. Software code induces physical state changes in material hardware, and digital structures have a direct foundation in the material world. Software has a physical entropy state. Constructs in virtual space (polygon meshes) are physically stored as arrays of bits on the memory chip, but are conceptually similar to molecules in that they are essentially geometric forms exhibiting properties of flexibility, restriction of movement and interaction with other forms (dynamic geometry). If a simulated network of ‘dynamic geometry molecules’ were to operate in a way that exploited a heat difference (agitation) to induce unidirectional motion and create ordered states, it would reduce entropy in both virtual and real space and operate in essentially the same way as a biological organism. The usefulness of such artificial chemistries to investigate living processes has received much attention (e.g. Dittrich et al. 2006), but perhaps the most promising target for ‘soft’ life is the simulation of replicating systems of heat engines, particularly ribozymes (Gaines and York 2016) and enzymes such as V-ATPase (Isaka et al. 2019). Although detailed modeling of single heat engines is currently possible, simulation of complex networks of units with roles in replication and metabolism would be a greater technical challenge in terms of processing power. One can even conceive of a ‘soft’ ALife system managing and feeding back with a ‘hard’ ALife system to create a self-sustaining and self-governing physical structure. This is conceptually similar to the mechanics of a large multicellular organism functioning under the influence of biochemistry and instructions operating at much smaller physical scales. Indeed, many biological organisms are composed of structures operating on different principles over vastly different scales, from molecules, cells, tissues, to organs, integrated to allow self-sufficiency and survival of the individual. Populations of such systems could also be subject to ‘virtual selection’, as errors in virtual nucleic acid sequences could create virtual mutations, affecting the construction of hardware, with only the fittest (most appropriately functioning) survivors able to construct further copies.

Thus, the biological definition of life suggested above may at first seem far removed from the field of ALife, but may find increasing relevance if artificial networks of soft and hard components using the heat engine principle can organize resources and become self-reliant, directly analogous to organisms. If this actually transpires, a key philosophical dilemma will be whether this can be considered ‘artificial’ or not, or whether a self-replicating phenomenon represents a post-artificial case of no 2. Other dilemmas may include epidemiological considerations and quarantine measures.

Conclusions

Life represents order emerging from unidirectional change forms that direct thermal agitation and excitation energy into catalysis of reactions perpetuating a negative entropy replication network. Life’s main requirement is the thermal bath and increasing entropy of the universe, and thermal agitation is particularly strong in the regions of the universe close to stars. Many star systems are now known to include planets exposed to an appropriate temperature such that liquid water and complex molecules almost certainly exist (Bovard et al. 2015). As the difference between living and non-living matter rest in differences in configuration under thermodynamic agitation, simple life forms – identifiable as such because their components change configuration states cyclically to perform tasks together in self-replicating networks – are likely to be extremely common throughout the universe. If a sample from another planetary body demonstrates organized structure associated with a suite of components operating on the heat engine principle, it would be a strong indicator of life.

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