

What life is: the conversion of thermodynamic disequilibria into directional motion

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Abstract

'Life' is traditionally defined by a long list of properties, but classifying structures as 'living' or 'non-living' would require a single recognizable difference. Recent 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 cellular replication. These molecules exhibit disparate structures, but share the principle of repetitive unidirectional conformation changes, driven by thermodynamic gradients, that produce directional motion. Here, life is defined as a process whereby matter undergoes cyclic, unidirectional conformation state changes that convert thermal agitation and excitation into directed motion, performing work that locally reduces entropy. The principle of conversion of thermal agitation into directed motion is independent of any specific chemical environment or any particular molecular structure; this definition should apply universally across biospheres characterized by differing biochemistries.

1 | Life as a property of matter

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). Many of these properties are exhibited by putatively non-living systems such as crystals, fire and hurricanes. Thus a broadly-accepted definition of life has proven elusive and is deeply controversial.^[1-3] Is a simple classification of 'living' vs. 'non-living' things reasonable?

Organisms, as material objects, consist of atoms and molecules and thus exhibit measurable physicochemical properties. As the matter comprising organisms can be subjected to empirical investigation, it is reasonable to expect that a distinguishing property may be detectable – a property inherent to the matter comprising organisms, yet not evident for non-biological matter. The crux of the problem lies in detecting a single process occurring at the molecular scale, but shared across a vast array of disparate molecules with extremely variable structures operating in tremendously complex networks.

However, 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 principle by which they operate. Intriguingly, it may be that we have already detected a property of matter that can explain the state of 'being alive', although we have perhaps failed to recognize just how pervasive this property is throughout Biology.

2 | Long-term vs. immediate processes defining life

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^[2,4]. Indeed, a recent definition of life as 'a *self-sustaining kinetically stable dynamic reaction network derived from the replication reaction*'^[5] 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.^[5]

However, life can also 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 braying. 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?

Erwin Schrödinger^[6] provided a crucial clue when he described life as 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, in biological systems a wide range of different types of 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 shift forms under excitation.

3 | Random vs. directed motion

Matter almost never stays still. Atoms and molecules vibrate, and the extent to which they do so, by definition, determines the temperature of a system. Thus, at temperatures above absolute zero, matter is always in motion. 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 exchanges. 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 of 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.^[9]

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 a range of possible conformations that are "sampled through motions with a topologically preferred directionality".^[10] Thus, thermal agitation and excitation can induce directional motions in certain 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^[10-13], the spinning sub-units of enzymes such as ATP synthase or V-ATPase spin in one plane^[14,15] to generate mechanical 'torque' that performs work^[16], catalytic RNA molecules (ribozymes) shift between conformation states^[17,18], the ribozyme components of ribosomes ratchet along mRNA to provide the driving force of protein synthesis^[19], and RNA polymerase similarly ratchets along the DNA molecule during transcription.^[20] Indeed, enzymes (catalytic proteins) exhibit conformational state changes, and the resulting physical motion is necessary to catalytic function as it facilitates substrate binding.^[21] Many non-motor enzymes are known to essentially produce 'directional mechanical force'^[22] or 'convert chemical energy into mechanical force'^[23] to perform work; directional motion, torque generation and power output thought to be general properties of asymmetric proteins.^[24] Thus, across a broad range of biological macromolecules, flexibility and asymmetry results in consistent, cyclic (repeated) motion and mechanical action that can dependably perform work.

While the motion of molecules is typically inferred from structural relationships and computer modeling, we can now directly observe the movement of molecules. High speed atomic force microscopy has recently 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.^[13] The myosin V molecule 'walks' hand-over-hand along the actin filament in what the authors describe as a 'unidirectional processive movement', 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.^[13] The extent and direction of motion are not simply constrained by interaction with the actin filament, but by the conformational states possible for the head domain: slight deviation in bending could result in attachment to actin subunits at incorrect distances or directions, or in attachment to neighboring actin filaments, any of which could result in a disastrous lack of function.^[13] The principle 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.^[25] Artificially designed ribozymes can even perform 'riboPCR' (i.e. copy RNA templates in a manner similar to the polymerase chain reaction, PCR^[25]). This range of metabolic and replicative activities is thought to be a prerequisite for abiogenesis, or the emergence of biology from chemistry.^[26,27] Like motor proteins, ribozymes also perform these activities via directional motion. For example, the Tetrahymena ribozyme includes a mobile motif (the 'tP5abc 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 just 10 and 300 ms, respectively.^[28] Thus ribozyme function depends on a single property: the ability to reliably switch between conformational 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.

4 | Life is an uphill struggle

The real biological systems presented above can all be considered, theoretically, as Feynman–Smoluchowski ratchets^[29] or 'Brownian ratchets'^[20]: i.e. systems for converting stochasticity into order. Brownian movements of molecules in part of the system affect regions of molecules that are free to move in one direction, but not backwards, effectively converting random movements into directional motion. At first glance this may seem to represent a perpetual motion machine, whereby background thermal agitation of molecules is inevitably converted into continuous progressive movement. However, this is complicated by the fact that excitation of the mechanism itself potentially dissipates energy randomly, and such a system is thought to be able to produce work only if the driving interactions are of a higher energy state than the components of ratchet itself,^[29] i.e. with a net 'energy input' or, more correctly, with a thermodynamic gradient or disequilibrium. As a proof of principle, it is possible to construct a physical ratcheting mechanism that converts non-directional fluctuating forces such as white noise into unidirectional rotation (i.e. a device that spins in a noisy environment).^[30]

Despite reducing entropy locally, such systems do not contravene the second law of thermodynamics (that entropy in a system always increases), because a relatively small decrease in entropy is connected to and driven by a larger entropy increase: i.e. a localized decrease but a net increase. Feynman–Smoluchowski Brownian ratchets are structured in a way that links one thermodynamic gradient with a weaker secondary disequilibrium, like a descending torrent driving a waterwheel that actuates a pulley system lifting a bucket uphill. More precisely, the mechanism is 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.^[31] 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^[31-33]. 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.^[31]

What, then, of the role of 'energy carriers' such as ATP? Crucially, while thermal agitation is the torrent that induces motion, ATP acts essentially by fixing the motion of biomolecules at a point far from thermodynamic equilibrium (i.e. ATP carries a disequilibrium).^[31,34] ATP is part of the mechanism that stops backward movement and favors advancement, but thermal agitation provides the driving force.

While many of these concepts have previously been acknowledged as fundamental to life^[20,31], 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 definition or theory of life.

5 | 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 structure). 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:

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

This process determines the immediate state of 'being alive', agrees with the concept of disequilibrium driving Feynman–Smoluchowski Brownian ratchets^[29,31], is a mechanism that aggregates matter to produce 'negative entropy'^[8], underpins the 'self-sustaining kinetically stable dynamic reaction network derived from the replication reaction'^[15], its components are subject to the further long-term processes of mutation and natural selection^[35], 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.

6 | Conclusions

Life represents order emerging from unidirectional molecular conformational changes that direct thermal agitation and excitation energy into catalysis of reactions perpetuating a negative entropy replication network. Thermal agitation of molecules, energy exchanges and entropy are universal phenomena, and many star systems are now known to include planets exposed to an appropriate temperature such that liquid water and complex molecules almost certainly exist.^[36] As the difference between living and non-living matter rests in differences in molecular configuration under agitation, simple life forms – identifiable as such because their component molecules change conformation states cyclically to perform tasks together – are likely to be extremely common throughout the universe. If a sample from another planetary body demonstrates organized structure associated with a suite of molecules capable of repeated unidirectional conformational state changes, it would be a strong indicator of life.

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