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Meaning of the Living State

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Introduction

Astrobiology is the study of life in the universe [1]. However, in spite of rigorous debate, the astrobiology community does not have an agreed upon definition of life [2, 3]. To make progress in the face of this conceptual issue, astrobiologists focus on specific properties of living systems, such as replication or cellular respiration [4, 5]. This has allowed researchers to make progress in limited domains, such as characterizing the emergence of Darwinian evolution or quantifying the detectability of biosignatures [6, 7]. Unfortunately, without a consistent definition of life, there is no clear way to integrate the progress from these domains into a better understanding of life in the universe or its origin on Earth. Here I elaborate on the emerging concept of the *living state,* which may provide a framework to enable such integration.

References to a *living state* can be found throughout origin of life and astrobiology science [8, 9, 10, 11, 12, 13]. For different authors, the *living state* often has different meanings and connotations associated with it. For some, this term appears to be a convenient linguistic tool, used to describe the phenomena associated with biology [10, 9]. For others, this concept is intended to characterize life as a unique class of nonequilibrium processes [8, 13].

Perhaps the earliest mention of the *living state* was by the Nobel Laureate biochemist Albert Szent-Gyorgyi. In 1941, he wrote two very similar manuscripts, one for *Nature* and one for *Science* [11, 12]. In both he argues that to make progress biochemists must probe the submolecular structure of biomolecules [11, 12]. In particular, he drew inspiration from the electronic properties of crystals and semiconductors which were just becoming clear thanks to advances in statistical and condensed matter physics [11, 14]. Szent-Gyorgyi was struck by the collective behavior of electrons in semiconductors and hypothesized that similar principles were at play in the function of biomolecules [11, 14, 15]. He suggested that the deepest mysteries in biochemistry would only be explained by appealing to submolecular considerations. He went on to posit that certain features of the *living state* may be consequences of quantum mechanical laws [11, 12]. For Szent-Gyorgyi, the *living state* could be distinguished from

nonliving states based on the collective behavior of electrons. Interestingly, he rejected this idea later in this career, but it has recently seen renewed interest from other researchers [16, 17].

Since this first use by Albert Szent-Gyorgyi, the term the has been used by many more authors [8, 9, 10, 13]. Most of these authors use the *living state* when discussing the origin of life on Earth. These authors chose to investigate the origin of the *living state* rather than the origin of living cells, or organisms. The adoption of this term may be due to the realization that the "atoms" of biology cannot exist in isolation, physically or conceptually [18]. The description of living systems requires a specification of a macroscopic (or at least mesoscopic) system, which not only contains individual components (such as cells or organism) but also the nature of their interactions and their environment [18]. Therefore, the *living state* is used to refer to the essential features of biological processes that are not strictly contained within individual objects but rather manifest in the interactions between objects.

This use of the term can be found in a review of the progress on the RNA world hypothesis by Higgs and Lehman [9]. The RNA world posits that RNA played a crucial role in origin and early evolution of life on Earth [19]. In an RNA world scenario, RNA molecules are assumed to have been, at some point, the primary information carrying molecules required for primitive genetics, as well as the primary enzymatic molecules required for primitive metabolisms. Higgs and Lehman describe the evidence for an RNA world as well as the processes which would be required for it to exist. They report progress on RNA nucleotide synthesis, describe various models of RNA polymerization, and explore the concept of molecular cooperation [9]. In that review the authors define the *living state* to mean a state of the world in which the processes of enzymatic nucleotide synthesis, polymerization, and recombination are coordinated in a such a way that RNA molecules are reliably and robustly produced. This *living state* is contrasted to the *dead state* where all those processes may exist in an uncoordinated or unorganized manner (see specifically box 3) [9]. Thus these authors use the *living state* to identify the global scale organization necessary for the persistence of the RNA world.

Other researchers have used the concept of the *living state* to explicitly place biological phenomena within the epistemological scope of statistical physics [8, 20]. Within this framework biological phenomena at a given scale of organization (say, the cell) are explained and understood by appealing to the statistical properties of the dynamics of the smaller scales *and* larger scales. This is analogous to how distinct states of matter are understood by appealing to the statistical properties of atoms, with the important distinction that statistical physicists have historically not included constraints from larger levels of organization, which are essential in determining the properties of living systems. This conception

of the *living state* may enable astrobiologists to integrate progress from different disciplinary perspectives into a quantitative theory of life. Living systems are influenced by many different processes, such as geological, geochemical, atmospheric, and astronomical processes [21, 22, 23, 24]. Understanding biological organization through the lens of the *living state* does not attempt to reduce all of these processes to physics but rather generalizes the approach of statistical physics to accommodate the diversity of phenomena seen in the biosphere. To understand how the tools of statistical physics can be used in this way, it is important to understand the history of that field.

A Brief Synopsis of Statistical Physics

The goal of statistical physics is to reconcile the microscopic behavior of atoms or molecules with the macroscopic properties of materials. In the late 19th century the foundations of statistical mechanics were developed by Ludwig Boltzmann, Josiah Willard Gibbs, and James Clerk Maxwell [25]. At the time, the laws of thermodynamics were still being established but the primacy of thermodynamic descriptions of natural and artificial systems were widely accepted [25]. By contrast, there were still debates about the legitimacy of atomic theory [25]. Boltzmann's goal was to advance atomic theory by showing it was consistent with the known laws of thermodynamics [25]. To that end, Boltzmann calculated the average properties of particles interacting according to Newtonian mechanics. By taking the limit where the number of particles gets very large, Boltzmann proved that his formalism reproduced the second law of thermodynamics. In essence he demonstrated that the second law of thermodynamics was a statistically guaranteed consequence of Newton's laws of motion applied to a very large number of particles. This was the first explicit demonstration that a macroscopic theory (thermodynamics) could emerge from coarse-graining (in this case by averaging) a microscopic theory (Newtonian Mechanics).

The emergence of a macroscopic theory from a microscopic theory can be understood from the example of the ideal gas law. Gases are composed of a very large number of molecules. Each one of those molecules obeys Newton's laws of motion and therefore can be described by its velocity and position. If the number of particles in the gas is N, the number of parameters required to describe the gas using Newtons laws would be 6N, because each molecule has components of its velocity in three dimensions, similarly for its position. For any large number of particles the information required to describe the dynamical properties of a gas could become huge. However, it turns out that as a larger and larger number of particles are considered, the statistical properties of the gas become highly constrained [26]. These statistical constraints guarantee that the system will have

certain features [26]. In the case of gases, those features are the pressure, temperature, and volume of the gas. In the thermodynamic limit, where the number of molecules goes to an arbitrarily large number, these features completely characterize the entire gas system [27].

By the early 20th century, atomic theory was widely accepted, thanks in part to Boltzmann and the development of quantum mechanics [14]. Around this time, research in statistical physics became organized around the concept of phase transitions [14, 28]. Some examples of phase transitions are the familiar phenomena of the melting of solid materials and the evaporation of liquids. Prior to the development of statistical physics, certain features of phase transitions were well understood experimentally [14]. For example, it was well known that pure metals had very specific melting points, thanks to the many industrial uses of metallurgy. However, experimental and theoretical interests in phase transitions were reinvigorated in the 1930s thanks to the discovery of superfluid helium and superconducting metals [14]. While the foundations of statistical mechanics and thermochemistry provided by Boltzmann and Gibbs had demonstrated that microscopic laws of motion acting on Newtonian particles could give rise to the macroscopic properties of materials, the study of phase transitions attempted to understand how the same microscopic laws applied to the same particles could give rise to such a diversity of macroscopic phenomena [29]. How was it that water molecules, subjected to the same microscopic laws of physics, could collectively exhibit the properties of a solid, liquid, or gas? The empirical facts provided by new phases of matter would elude theoretical explanation for most of the century [14, 30].

Quantum mechanics had provided a description of single (or few) electrons and their interaction with hydrogen nuclei, but these new phases of matter presented novel patterns in large systems with many electrons. These phenomena were some of the first examples of collective behavior in physics [30]. Understanding these processes required a set of theoretical tools known as the Renormalization Group (RG) [30]. The RG was developed simultaneously in statistical physics and quantum field theory [28, 30]. Initially these techniques were implemented in an ad hoc manner to deal with infinities that emerged in quantum field theories. However, the subsequent formalization of RG thanks to Freeman Dyson and later Kenneth Wilson demonstrated that RG techniques need not be ad hoc. The modern understanding of the RG is that it represents a set of tools to describe how different theories transform into each other when viewed from different perspectives [28, 29, 30].

Distinct states of matter emerge from similar microscopic systems because the collective behavior of the microscopic parts changes as larger and larger systems are considered [29, 30]. For example, the key difference between steam and liquid water is that individual molecules in steam have velocities seemingly

independent from one another, whereas in the liquid state they are strongly correlated. This difference is not obvious at the microscopic scale. When observing a single molecule, whether in the gas or liquid, its motion will be correlated with the other molecules nearby due to intermolecular forces. However, as we consider more particles, the effect of this correlation tends towards zero in the gas because particles rarely interact in gases due to their low density. Meanwhile, in the liquid, with its higher density and therefore the higher interaction frequency, the effect of these correlations tends to increase. This qualitative difference (between zero and non-zero correlation) emerges as a consequence of quantitative differences in the microscopic dynamics and is responsible for the different macroscopic properties of the two phases [29]. In the study of phase transitions, these qualitative differences are usually tracked using *order parameters,* which are macroscopic properties that distinguish between different states. Often order parameters will take on a value of zero in one phase and a non-zero value in the other [28, 30].

The history of statistical mechanics is a story of reconciling different descriptions of nature. Equilibrium statistical mechanics was successful because Boltzmann demonstrated that the laws of thermodynamics emerge as a consequence of the dynamics of many-particle systems [25, 29]. Those properties, which are statistically guaranteed by the microscopic dynamics, end up defining thermal states at the macroscopic scale [26, 30]. The renormalization group demonstrated how systems with similar microscopic dynamics can result in different macroscopic states by formalizing how descriptions of those microscopic dynamics change as they are probed at different sizes or scales [29]. In summary, as a scientific enterprise, statistical physics in the 20th century provided answers to two very general questions [29]: (a) What are statistically guaranteed consequences of a given set of dynamics? and (b) under what circumstances do those consequences change? As a conceptual framework, the *living state* attempts to leverage these theoretical advances to integrate progress from many different fields into a coherent theory of living systems.

Life as a State of Matter

Using the theoretical approach of statistical physics to investigate biological phenomena provides an opportunity to reconceptualize our understanding of biology. The notion of the *living state* emerges in the attempt to realize that theoretical approach. The *living state* is defined by the collection of all statistically guaranteed properties associated with the biosphere, in the same way that the gaseous state is defined by the pressure, temperature, and volume of the container. The framework of the *living state* does not necessarily propose a definition
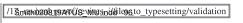
of life but rather a description of the features of life on Earth that are relevant at the large scale (both space and time). Currently there is no scientific consensus around which statistical properties must be associated with the biosphere; however, some suggestions include the topological properties of biochemical networks [31], interactions between the biosphere and abiotic surface processes [32], and the flow of electrons through organic matter [8]. This prospective has led many researchers to reevaluate established empirical data, as in [20], and it has led to new scientific questions [31, 33].

In the study of thermal states, the relevant properties emerge as the number of particles approaches 10^{23} (one mole). It is still not clear how to determine the appropriately large scale at which the relevant features of the *living state* emerge. Biologists study living systems at a number of different length and energy scales, from the molecular to the ecological. Recent advances in DNA sequencing, metagenomic analysis, and information sciences have enabled scientists to develop databases that span all of these scales [31]. These global databases have opened the possibility of studying life on Earth at the scale of the entire biosphere [8, 31, 32, 34, 35]. These studies have led some authors to suggest that the relevant features of the *living state* only emerge at the scale of the entire planet.

Viewing biological phenomena as a planetary scale processes represents a radical departure from many traditional perspectives in biology [36]. For example, Falkowski et al. argue that one of the most important features of the *living state* is the way in which it facilitates global scale cycling of material and energy by interacting with geological and atmospheric processes, which occur at a scale much larger than individual cells or populations [32]. They argue that these processes emerge not due to the dynamics of individual organism or even species. Instead they suggest that horizontal gene transfer is one of the key dynamical processes that statistically guarantees those features of the biosphere [32]. Prioritizing the role of horizontal gene transfer stands in stark contrast to most work in biology, which emphasizes the role of evolutionary dynamics by vertical descent in shaping the relevant features of living systems [36, 37].

While some researchers have suggested that the defining characteristics of the *living state* emerge at the scale of the biosphere, others (including myself) have suggested that the defining features of the *living state* emerge at many scales, not just one [31, 38]. We recently demonstrated this concept using biochemical reaction networks, which were constructed using genomic data [31]. We analyzed over 28,000 networks across three different scales of organization. We used individual genomes to construct networks for organisms, metagenomes to construct networks for ecosystems, and every known biochemical reaction to construct a network for the entire biosphere. By comparing the statistical features of these networks, we found that they shared certain properties that could not be explained simply by the shared rules of biochemistry (which are determined

according to mass balance) [31]. These features appeared in genomes from different evolutionary domains, in metagenomes from different environments, and in the biosphere as a whole. The ubiquity of these features suggest that there may be underlying dynamical laws out of which these emerge as a statistical guarantee.

As the essential features of the *living state* are better characterized and understood they will help inform our understanding of the origin of life. In the context of the *living state,* the origin of life has a natural interpretation as a phase transition [8, 33]. Just as in thermal states where the laws of physics are the same for molecules in a gas or a liquid, the laws of organic chemistry are the same for carbon in the *living state* or in the nonliving state, but the macroscopic consequences of those laws are very different. Understanding how these macroscopic differences manifest will require identifying the relevant order parameters for distinguishing the living and nonliving states.

Contemporary research in the origin of life suggests a few candidate order parameters [8, 33]. Smith and Morowitz have argued extensively that the origin of life on Earth emerged as a response to planetary scale disequilibria [8]. This chemical disequilibria is due to the extremely different oxidation states of the Earth's mantle and atmosphere, where the relatively reduced mantle is much richer in electrons than the relatively oxidized atmosphere. They argue the biosphere dissipates this disequilibria by facilitating the flow of electrons from reduced sources in the mantle to oxidized sinks in the ocean and atmosphere. Accordingly, they suggest that the flow of electrons through organic carbon may be a key order parameter for the *living state* [8]. This conclusion is remarkably similar to Szent-Gyorgyi's original hypothesis that the collective behavior of electrons is responsible for the *living state*.

In my own work I have demonstrated that the origin of lifelike properties may be effectively tracked using information theoretic quantities [33]. We developed a chemical kinetic model of primitive replicators that are strongly coupled to a dynamic environment. In that model we observed two stable states, which dynamically emerged. In first state, labeled the non-life state, few replicators exist, and they are not selected according to their fitness. By contrast, the life state is dominated by replicators that were dynamically selected according to their fitness. To characterize the relationship between replicators and their environment we employed mutual information, which is a nonlinear measure of correlations. We saw that the transition from the non-life to the life state was tracked by these correlations, consistent with the idea that the *living state* is characterized more by the relationship between individual components rather than the components themselves [33].

Both features of the biosphere discussed here—life's interface with geochemical processes and the universal features of biochemical networks—may

be independent of the particular of the details of terrestrial biochemistry. Any living system would be expected to interface with its planetary environment, and the universal features of biochemical networks cannot be explained by their shared biochemistry. Similarly, the two candidate order parameters for the living state discussed here do not require specific information about life on Earth. Accordingly, these features should be of great interest to astrobiologists who seek to understand life as it could be, not life as it is on Earth. The key to understanding the relevance of these features to biological organization lies in viewing life as a state of matter that manifests at many scales, not just at the scale of individual cells or organisms. By adopting this framework, astrobiologists can exploit the powerful theoretical tools and techniques of statistical physics to develop a theory that explains the interactions between the many biological and abiotic scales organization that characterize life on Earth, and (potentially) elsewhere in the universe.

Conclusion

The *living state* is defined by the collection of statistically guaranteed properties associated with the biosphere. This concept emerges when scientists attempt to apply theoretical concepts from the field of statistical physics to characterize biological systems. Adopting this prospective leads to new scientific hypotheses regarding the nature of life on Earth as well as its origins. These new research directions assume that "life" is a phenomena that manifests at a macroscopic scale and attempt to identify the key parameters characterizing that phenomena. These features may be independent of particulars of Earth life's chemistry and would therefore be useful in guiding searches for life beyond our planet. Thus, the concept of the *living state* may prove fundamental in the future of astrobiology.

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