

Comment

Self-Generated and Reproducible Dynamics in “Gene Years” Represent Life

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In a recent article (1), Trifonov has developed an approach, conceptually inspired by principal component analysis (PCA), for arriving at a consensus definition of “life” as “self-reproduction with variations”. In appreciation of the sound analytical effort applied rigorously on a comprehensive body of literature, I will refer to both the approach and the definition as “Trifonovian”. The Trifonovian approach has to be commended in its effort to evolve a minimalistic, and at the same time an *all-inclusive*, definition of life. In fact, from the literature on molecular components of living systems, the Trifonovian definition of life is clearly a direct reflection of the ideas of “consensus” sequences at the level of DNA/RNA and (in specific cases) even proteins, and homology modeling (including minimal functional “motifs”) in protein structures. Thus, while appreciating the Trifonovian approach, it is also important to carefully consider the severe limitations of consensus/similarity approaches (applied for the molecular components) that have pushed the limits of experimental (both computational and wet-laboratory) biology into increasingly complex/sophisticated formalisms that have unfortunately not provided universal insights till date. In fact, some universal insights have been achieved only by comprehensive (computational and/or wet-laboratory) rather than consensus based approaches (2-5).

Limitations of the Trifonovian Definition of Life

A definition is expected to “explain” (and not just summarize) the meaning of a term. Scientifically, a definition has to be able allow extraction of parameters that will enable a mechanistic understanding of the term in view of the scientific method of “Observation → Hypothesis → Experiment → Mechanism”. Thus, the obvious question arises – why is a definition of life required? My answer to this question involves the following aspects – A definition should allow (a) extraction of parameters, open to theoretical analyses and/or experimentation (computational/wet-laboratory), useful in providing mechanistic insights into life – eventually leading to “rules” that can allow classification of a system as living or non-living, and, (b) a clear establishment of both necessary and sufficient requirements to be able to not just provide an understanding on the origin(s) of life but also lead to methodologies towards synthesis of life *de novo*. In this regard, the Trifonovian definition fails to address the above aspects either partially or in totality. For example, “variation” in the definition of life is subject to variation in the environment. If the environment was a static/stagnant variable, then “variation” in the definition of life would not be required (since “variation” in life is not observed in a static/stagnant environment). Further, the Trifonovian definition fails to address the molecular dilemma in realizing self reproduction within the constraints of conservation of mass and energy (*i.e.*, exchanges with

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the environment must be built-in). On a trivial (and somewhat philosophical) level, the Trifonovian definition fails to classify “sterile” living systems (*e.g.*, male mules) as a part of “Life”.

Molecular Outlook for Developing a Definition of Life

Extending the spirit of appreciating a requirement for the definition of life, let us carefully consider our understanding of a living system from the molecular perspective in terms of a unit of life, *i.e.* a cell. Figure 1A shows the basic molecular machinery of a unit of life. The molecular entities involved in giving a cell its identity as a living system in terms of

the central dogma (6) are shown, though a few recently discovered exceptions to the central dogma have been reported recently (7-9). A living cell has evolved through presence of a single or several proteins resulting in phenotypic traits that are retained or lost in response to environmental changes. Interaction between the components of the proteome and the environment results in governing the dynamics and balance of the proteome to keep the cell as a unit of life in a given environment. Coding to construct this proteome is well guarded in two layers of code, neither of which readily interacts with the environment. “Variations” in this unit of life, in response to environmental changes, can result from either the feedback from the proteome to the genome, or, interaction between the

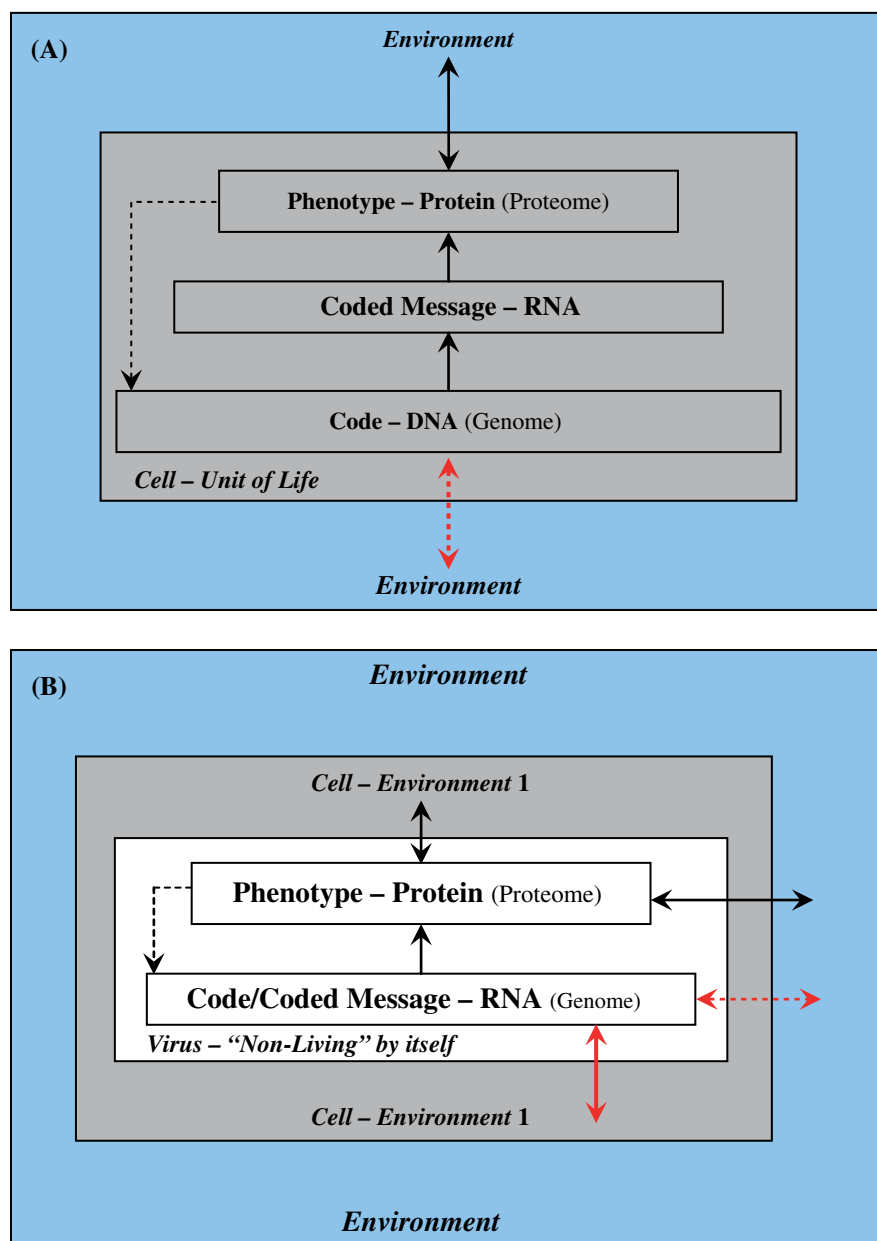


Figure 1: Molecular understanding of life and evolution. (A) A cell, considered (and defined) as a unit of life, is shown as a grey box. The molecular entities involved in giving a cell its identity as a living system in terms of the central dogma are shown. The environment is shown as a blue box. Components of the proteome interact with the environment (shown by bi-directional black arrow). Coding to construct this proteome is well guarded in two layers of code, neither of which readily interacts with the environment. “Variations” in this unit of life, in response to environmental changes, can result from either the feedback from the proteome to the code *i.e.*, the Genome (shown by the uni-directional dashed black arrow), or, the more direct interaction between the code and the environment (shown by the bi-directional red dashed arrow). (B) An example of RNA virus (white box) is shown, where the code/coded message interact with two levels of environments (cell - grey box: Environment 1, and the Environment of the cell/free-virus itself), in addition to the interactions of the proteome.

code and the environment. The former is responsible for accumulating variations over time leading to the slow process of evolution. For example, a protein not involved in interaction with the environment is gradually not present in a form to provide any feedback and thus is not further synthesized from the code. The resulting loss of this protein inside the cell gives rise to different phenotypic traits (variation). However, if the latter was possible, substantial variations would be observed in living systems at very short time scales. Even more drastically, in many cases life would not self-reproduce, since substantial variations would occur even with minor changes in the environment. Simply put, if the code was directly interacting with the environment, minor changes in the environment would yield sufficient changes in the code that could be amplified to form new life forms, rather than self-reproducing life forms. Every reproduction cycle would give rise to a new life form. Figure 1B shows an example of RNA virus, where the code/coded message interact with two levels of environments, to support the above. For the virus, cell is the first level of environment that it has to interact with, referred to as Environment 1. However, since the virus has direct interaction of the code with its environment in addition to the proteome interacting with the environment, changes in the living form of virus is observed at very short time scales. This is true for all known RNA viruses (without exception). Thus, it is essential to appreciate that it is the phenotype that interacts with the environment, and only those living systems have survived (or will survive) in terms of self-reproduction in which the genotype (*i.e.*, the code for creating phenotype) is not (or minimally) capable of interacting with the environment.

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Based on the above discussions, and inspired by the Trifonovian approach, it is desirable to utilize the comprehensive body of literature for arriving at a definition of life. However, it may be more useful to extract some universal concepts/principles discussed in Trifonov (1). It is clear that two key features must be built into a definition of life: Kinetics and Self-assembly.

Note that I have specified the two features in form of parametric variables that can be scientifically explored. Definition of life must specify its ability to self-generate (rather than self-reproduce with variations in response to the environment). The term “self-generation” accounts for a variety of self-assembly processes within living systems. The terms “reproducible dynamics” account for organized kinetic processes required for maintenance and self-generation properties of living systems. They also signify the importance of reproducing the dynamics, rather than the individual components behind the dynamics. In fact, at a molecular level, several features observed in and/or for living systems show dynamic behavior that, while stochastic in the actual initiation, follow clear and systematic kinetic modes from starting of an event to their completion regardless of the system and the technique (10-12). Finally, I would like to propose that analogous to the astronomical unit of “light years” (for length-scales in the universe) it will be useful to develop an evolutionary unit of “gene years” that can allow an understanding of time-scales for evolution of life and length-scales for genomes in the proposed definition of life.

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