A framework for investigating Rules of Life across disciplines

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ANTECEDENT QUESTION: What is a clear and useful definition of "Rules of Life" and how can we use such a definition to develop a conceptual framework that allows investigation of Rules of Life across disciplines and hierarchical levels of organization in life systems?

The National Science Foundation (NSF) has invested heavily in ten "Big Ideas" in science and engineering (https://www.nsf.gov/news/special_reports/big_ideas/). The Big Idea most closely aligned with the Biological Sciences is "Understanding the Rules of Life," which is described as "elucidating and harnessing the sets of rules that predict an organism's observable characteristics, its phenotype." Yet living systems are constrained and shaped by rules that influence biological processes operating at multiple hierarchical scales from atoms to ecosystems, and the emergence of phenotype, while a critical question, is most directly relevant to only a small fraction of the disciplinary scope encompassed by the biological sciences.

Despite the importance of identifying critical biological rules and how they operate within life systems, the meaning of the phrase "Rules of Life" is, at this point in time, ill-defined. "Rules of Life" is used by different people to refer to different (and often non-specific) subsets of the governors or drivers of any important aspect(s) of life. In the absence of a more rigorous definition, scientists and policy makers struggle to understand, precisely, how research on Rules of Life can be differentiated from other types of biological research. Articulating a clear definition of "Rules of Life" that is applicable across biological disciplines will facilitate more rigorous thinking regarding the role of *rules* in biology, potentially leading to an improved capacity to predict the dynamics of living systems including, but not limited to, the emergence of phenotype.

Defining Rules of Life

On any field of play, rules serve to constrain potential actions of the players. In the context of life, then, if we assume that the "field of play" is planet Earth (or, perhaps even the universe), we can define the "rules of life" (ROL) simply as the *set of potential constraints on the operation of life systems*. Using a common dictionary definition of "rules" as a basis to identify "Rules of Life" is, admittedly, more philosophical than scientific. Yet we argue that such a definition is useful. The definition is broad enough to incorporate rules that operate across most of all disciplines of biology and hierarchical scales of organization in life systems, but specific enough to define a type (and therefore subset) of governing aspects of life systems as the Rules of Life.

Association with mechanisms

If ROL govern the operation of livings systems, individual rules (constraints) must be tightly associated with specific mechanisms by which biological systems meet the requirements for life. When two biological systems use the same mechanism to fulfill a requirement for life, they are both subject to the constraints associated with that mechanism. Yet if two biological systems incorporate two different mechanisms to fulfill the same requirement for life, one system is subject to the constraints governing the first mechanism, and the other system is subject to the constraints governing the second mechanism. For instance, a simplistic example might be that any form of catabolic metabolism can provide energy required to sustain life. However, methanogens operate under a different set of constraints than aerobic heterotrophs to achieve a similar requirement. In a less trivial example, the evolution (or bioengineering) of cell membranes that can operate at a pH lower than existing membranes would relax some ROL that constrain life systems that rely upon membranes. Yet if additional, new constraints are associated with the novel membrane structure, any system that relied upon that the novel membrane would be subject to these new constraints.

Rules of Life and the paradox of holarchy

Taken alone, the tight coupling between the mechanisms used by life systems and the constraints on those mechanisms is hardly a novel idea, and is perhaps even obvious enough to be considered trivial. However, biological systems are fundamentally hierarchical and nested ("holarchies"). At any level of organization within a holarchy, a holon (a system observable at a particular level of organization) is: 1) comprised of components that operate as systems (holons) themselves at a finer scale, and; 2) encompassed by and a component of holons that exist at a coarser spatial scale. The tight coupling of specific rules to specific mechanisms thus requires that *ROL must operate at the same hierarchical level of organization as the mechanisms they govern*.

This principle creates a paradox: although any ROL must *operate* at a specific level of organization, the *effects* of ROL undoubtedly extend across levels of organization. For instance, genetic mutation (operating at the molecular level) and natural selection (operating at the organizational level that describes interactions between organisms and their environment – i.e., the ecosystem level) are both important mechanisms linked to evolution, which itself is a mechanism that operates at the scale of populations. Therefore, any constraints on mutation *must* act at the molecular scale while constraints on selection *must* operate at the ecosystem scale. Ultimately, however, some of the effects of constraints on selection and mutation *manifest* at intermediate scales, i.e., changes in the characteristics of populations, or, given enough time, the origin of new species.

Developing a general framework to describe how Rules of Life are subject to this paradox of holarchy represents a key challenge for biological research on the Rules of Life. We believe that there exist discoverable (and perhaps even a surprisingly small set of simple) means by which the effects of the Rules of Life cascade across and interact among levels of hierarchical organization in living systems.

Experimental Investigation of Rules of Life

In order to facilitate interdisciplinary and transdisciplinary investigation of Rules of Life, we believe that a framework of ROL is necessary, that describes how rules manifest effects that interact across levels of organization to regulate the processes and dynamics critical to the evolution and maintenance of life. The framework must be general enough to be independent of the scope of any single biological discipline, while specific enough to pinpoint critical uncertainties and guide research within each biological discipline. By our definition, these ROL represent constraints that operate at a specific level of biological organization. Therefore, a successful framework would account for the modular and fractal nature of life-system holarchies, yet also allow for multiple competing hypotheses that describe the means by which *effects* of ROL can cascade and interact across levels of organization and drive responses in biotic systems that manifest and are observable at different levels of organization. Perhaps most importantly, the framework must be able to generate *specific predictions to test hypothesized mechanisms by which the effects of ROL cascade across and interact among structural and functional scales of biological organization.* In facilitating such predictions, the framework would provide a basis for designing experiments that span and integrate disciplines to test our understanding of the means by which Rule of Life shape life systems.