Title: Characterizing the zones of influence for biological phenomenon across temporal, spatial and biological hierarchies

Question: How does expression of a phenomenon influence the expression at other hierarchical levels? Further, how far does the zone of influence extend across the hierarchy?

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Summary:
The ability to investigate a phenomenon across temporal, spatial, or biological hierarchies is essential for revealing basic 'rules of life'. Yet, phenomena occur differentially over levels of temporal, spatial, and biological hierarchies. Here, we propose a conceptual framework for characterizing the influence of a given outcome or process on other levels within a hierarchy.

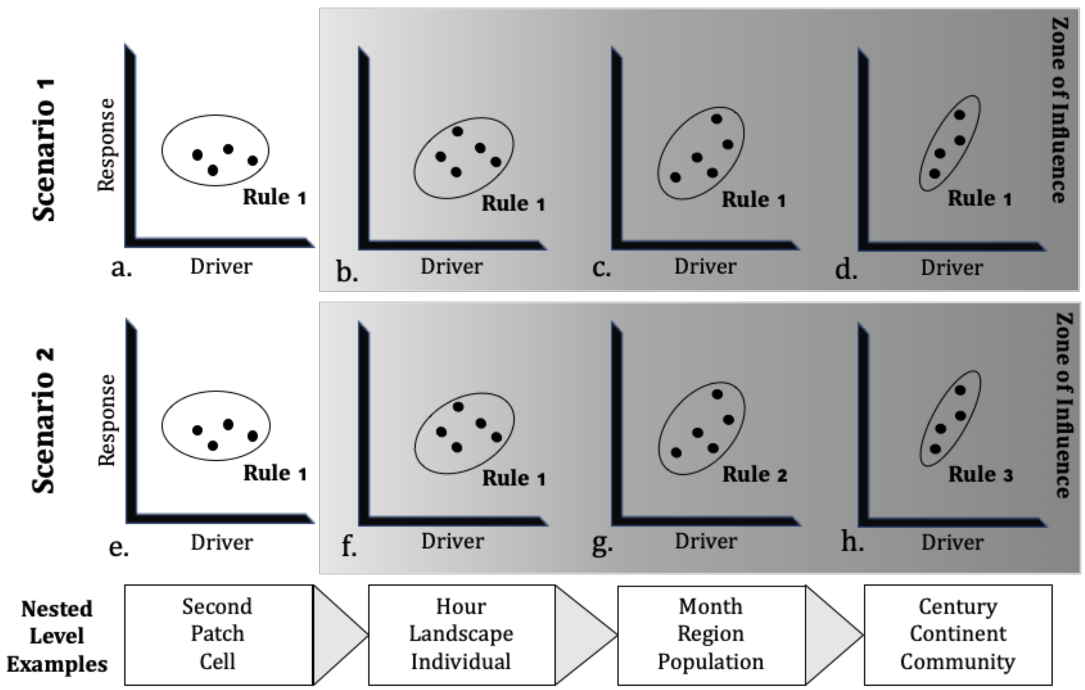

Figure 1. Scenario 1 (a-d) illustrates a biological phenomenon at multiple levels of a nested hierarchy, driven by a common underlying process (Rule 1). Scenario 2 (e-h) shows the same but with different underlying processes (Rules 1-3). The third row illustrates examples of several relevant nested hierarchies including time, space and biological hierarchies. The gradient background represents the zone of influence across level 2, 3, and 4 of a hierarchy. Darker color represents a stronger influence and the lighter color represents weaker influence.

What's the big question? What's the exciting science?

Biologists have long endeavored to identify general laws that govern life across time, space, and all levels of biological organization. Despite this interest in a unifying theory of biological processes, we have yet to find a theory that satisfies this academic longing. We argue that our ability to integrate across scales has been limited by a myopic attempt to find a single unifying principle regulating biological processes at all levels (e.g. Figure 1- scenario1). We propose a new conceptual framework. Here, we define the extent of time, space, or a biological hierarchy that is modified by a phenomenon as a “zone of influence”; a phrase that describes a continuum of effects that need not be generated by the same mechanism as we move across a hierarchy. For example, Figure 1 illustrates a biological phenomenon at multiple levels of a nested hierarchy, and in scenario 1 the same driver regulates a response across the entire hierarchy. In scenario 2, the responses at higher levels are influenced by different factors (e.g., Figure 1f-h). Note the effects of a process can intensify over a hierarchy because of the compounding of lower level responses (see shading in Figure 1).

These zones of influence allow for prediction of a range of outcomes expected at different levels of organization by providing a scope over which researchers can scale a phenomenon. This conceptual framework is valuable for two reasons. First, it acknowledges that there may not be a single unifying principle that can cut across all levels of biological organization, while simultaneously describing the space over which we may successfully scale up and down processes. Second, this conceptual framework allows for the comparison of hierarchical spaces over which different biological processes function in similar or potentially very distinct ways. Figure 2 shows one way to compare changes in effect size for biological phenomena across levels of hierarchy. The zone of influence is shaded and the strength of influence is greater as the effect size increases. The position, variation, and association between change in effect size and change in level of hierarchy indicate whether a biological phenomenon is scale dependent (Figure 2a), idiosyncratic (Figure 2b), or universal (Figure 2c).

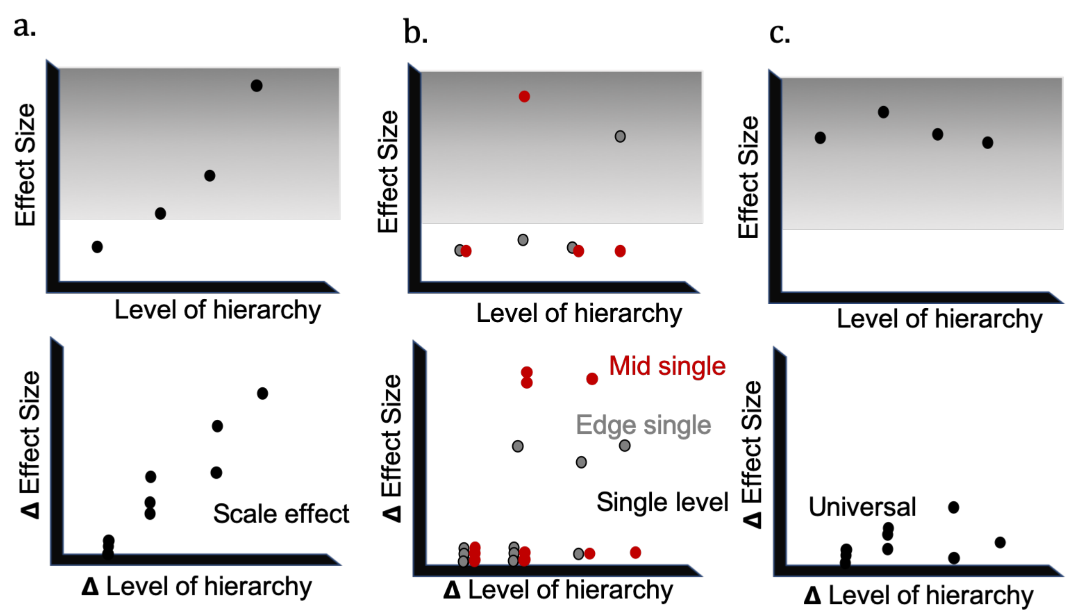

Figure 2. The effect size by level of hierarchy and the difference between all pairwise comparisons of the effects and levels of hierarchy for three different scenarios: a) the effect of the biological phenomenon varies across levels of hierarchy (Scale effect), b) there is a single level that has a strong effect (Single level) on the lowest or highest level of the hierarchy (Edge single) or in a middle level (Mid single), c) there is a cross-cutting effect (Universal). The biological phenomena approaching a “unifying rule of life” are cross-cutting phenomena and will show little to no variation in effect size across levels of hierarchy.

What's the potential impact?

Understanding the zone of influence of biological phenomena across a hierarchy can drive new scientific inquiry. For example, new research might explore the spaces within and the boundaries between zones of influence or contextualize and inform findings across scales. Indeed, this framework may also facilitate better integration of research on model organisms and within model systems to address questions in non-model and natural systems by allowing researchers to ask if their research questions fall within relevant zones of influence with regards to their desired inferences. Understanding where we can integrate across scales allows us to gain a broad understanding of the influence that perturbations have on biota at multiple levels of time, space, and biological hierarchies.

Why now?

The rapid and accelerating accumulation of data and biotechnologies has far outstripped our ability to achieve meaningful synthesis of the mechanisms that regulate biological processes across spatial, temporal, and biological hierarchies. The need to better understand how perturbations of biological processes are propagated across hierarchies is increasingly important in the face of impending climate change. The ability to extrapolate allows for improved predictions of how various temporal variables, spatial variables, and biological levels of organization, are influenced by biotic and abiotic factors, which may allow for mitigating large-scale effects.

What are the state-of-the-art technologies, applications, etc ...?

We now have the raw data to investigate linkages between hierarchical levels for many biological phenomena. This is partly because of the development of large synthetic datasets archiving genetic, morphological, distributional, and evolutionary history (e.g., GenBank, IsoBank, MOM/PanTHERIA, PBDB, Neotoma, GBIF, etc.). Additionally, the availability of sufficient computing power and statistical tools has drastically improved our ability to conduct complex hierarchical analyses. Even five or ten years ago, this would not have been possible. The field of biology has progressed from a time where it was difficult to generate data, to where the limiting factors are the conceptual framework, time, and incentive for synthesis.

Elaborate the key barriers and challenges that will need to be overcome.

Both technical and cultural challenges arise in integration across scales. First, how does one identify relevant phenomenon of interest that may be operating via different rules across scales? While there are many possibilities, not all are biologically important across all levels of hierarchy. Moreover, what are the key measurable traits or relevant parameters necessary to address? Although some phenomena may appear to be important, they may not be tractable. Additionally, what is the appropriate hierarchical axis along which the phenomenon should be scaled? This axis might be temporal (e.g., femto-second to peta-second), spatial (e.g., laboratory mesocosm, pond, lake), or biological (e.g., cell, individual, population, community). An additional set of technical challenges arises from standardizing how we measure phenomenon along hierarchical axes. Cultural challenges include significant differences in scientific approaches, methodologies, and even language. Creating a common framework and lexicon is essential for true biological integration, and is likely to increasingly become a problem when standardizing data across hierarchical axes.

What might be broader impacts?

Our biological knowledge is incomplete. The ability to integrate across hierarchies will help establish whether there are fundamental biological ‘rules’ that govern life. Our framework differs from others in that universal rules are not a prerequisite. The zone of influence framework can be employed by biologists across all fields to answer questions about the extent that phenomena can be studied in a common framework and whether findings can be scaled up or down levels of hierarchy or complexity, over space or through time.

Another broader impact lies in the training of future generations of scientists to be more comfortable tackling and solving complex interdisciplinary problems that may have implications across scales. Many of the important challenges of modern biology lies at the interface of disciplines; training students to employ conceptual frameworks, like the one we propose, enhances their ability to answer these types of questions. As we face the inevitable impacts of changes in diversity and non-target effects of synthetic biology, identification of zones of influence might allow us to better understand how introducing new genes, species, or traits will affect ecological and evolutionary processes.

How does it reintegrate biology?

Biologists tend to work in comfortable intellectual spaces with like-minded colleagues, usually within or along a single hierarchical axis - be it temporal, spatial or biological. Working at multiple and potentially interacting hierarchies requires a different set of approaches, skills and techniques. For example, a focus at the individual level of organization might mean examining the physiological response of a perturbation, or characterization of the type of selection the population is operating under. Working at a macroevolutionary scale involves study of the emergent properties that arise from the populations of populations; these might not be obvious from the intrinsic traits of the individuals. Thus, a different and unique set of theoretical, empirical and statistical approaches and tools might be necessary to integrate across these levels. Using the same conceptual framework allows characterization of the extent and boundaries of the zone of influence for all biological phenomena.

Temporal, spatial, and biological hierarchies are interrelated. Understanding these relationships is a natural secondary step in the development of the described conceptual framework, after establishing and testing the zone of influence. This secondary step is important because these three hierarchies necessarily interact.

What disciplines might be needed?

Scaling across a hierarchical axis involves multiple disciplines; the specific disciplinary knowledge required varies depending on the phenomenon under investigation. For example, quantifying patterns of body size across temporal, spatial, and biological hierarchies requires input from paleontologists, phylogeneticists, population geneticists, and evolutionary developmental biologists. Similarly, integrating a developmental process across levels of organization requires the input of not only developmental biologists, but also population and community ecologists, as well as evolutionary and systems biologists. Thus, integration facilitates interdisciplinary collaborations, fosters innovative ideas, and broadens the impact of the resulting outcome.

Intended audience of the paper

Our intended audience consists of scientists interested in exploring the integration of biological phenomena across time, space, and biological hierarchies. We can envision this framework intriguing many scientists, including but not limited to molecular biologists, landscape ecologists, paleontologists, neuroscientists, immunologists, and theoreticians. We expect papers that employ the zone of influence framework will have an even broader audience. Moreover, those that go even further by incorporating predictive modeling derived from zones of influence will likely be of interest to funding bodies, policy makers, and the general public.