

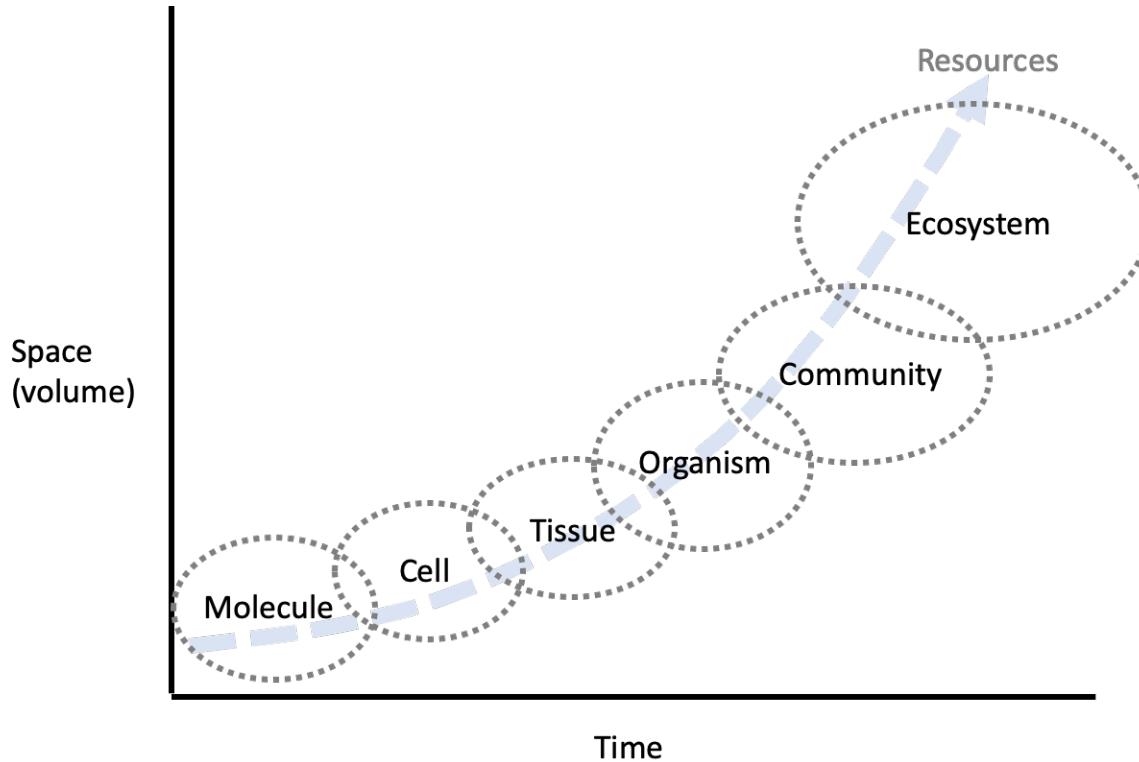
# Dealing with varying resources: a metabolic view of life across scales

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## INTRODUCTION

Although biology has benefited from a high degree specialization into several sub-disciplines, this compartmentalization now presents challenges to integrating across scales of inquiry. In order to better address integrative questions, a common language must be synthesized that can connect across a wide range of scales. To form this language, we need to connect intellectual structures that span current biological silos by crossing biological scales in time and space. The first step is to understand whether there are scale-invariant properties of life, followed by identifying *resources* that span all biological scales (Fig. 1). Independent of the existence of truly scale-invariant processes, we shall unequivocally reach a common vernacular that may be used to compare how rules of life occur at a hierarchical scale. If there are scale-invariant properties, information gathered at any one scale immediately provides us with the insights across scales. On the other hand, if there are no scale-invariant properties, we shall develop tools and methodologies that can be used to search for commonalities in any biological system and model and understand the basis for scale dependence. By framing hypotheses about life in a common vernacular, a domain specialist working at one scale should then be able to instantiate domain-specific predictions from theories that emerge from multi-scale perspectives on the rules of life in general.

This vision paper addresses the initiative of reintegrating biology sponsored by the National Science Foundation with the overarching goal of fostering innovative approaches towards interdisciplinary collaboration and communication. More specifically, we focus our discussion on the antecedent question, “What are the resources that span biological scales?”, which was developed in response to the following question, “How do biological traits and phenotypes scale across life?”.



**Figure 1.** A conceptual view of life that crosses time and space scales from molecules to ecosystems. We suggest that there are *resource* types that exist across scales, including free energy, forms of energy storage, and information. We also consider scale invariance in the concept of conductance (i.e. the capacity for movement of energy and materials between entities at a given scale). Moreover, scale-independent hypotheses allow for clear communication between research groups answering questions at different scales. In the tables, we describe some specific examples of using these resources to cross biological scales.

## Definitions and Terminology

**Energy** is defined as Gibbs free energy or free enthalpy (Greiner et al., 1995).

**Conductance** is the capacity of a system to generate rate and flux (Jarvis , 1995).

**Storage** is a concept of time and space. Storage represents the net accumulation of material and energy from incoming and outgoing fluxes (Leuning et al., 2012).

**Information** is taken as an index of potential variation in a system that can act to organize that system (Dusenberry 1992). We follow Stonier's (1990, 1996) view that information can be stored at any level of organization. As Stonier (1990) states: "The non-random distribution of atoms and molecules in living systems, that is, the intricate organisation of matter and energy which makes possible that phenomenon which we call life, is itself a product of the vast store of information contained within the system itself." (pg 13; Stonier 1990).

Prior to even beginning to delve into the impact of resources and the limitations of said resources on our existing predictive models of science, it is crucial to define resource types that exist across scales. Thus, we need to agree on a common set of *scales* as well as a common set of *resource types* that can operate idiosyncratically within those scales while still having characteristic similarities across scales. For this purpose, we identified six primarily biological scales depicted in Fig. 1 (Jarvis, 1995), ranging from that which could be defined under the smallest physical and temporal scales (molecular scale) to that defined under the largest spatio-temporal scale (ecosystem scale; Fig. 1). These scales do not necessarily reflect every biological scale that may exist in our universe but rather represent a general distribution of biological entities and processes in life as we commonly understand them.

Next, we identify resource types that can be identified at any scale. We propose that two principal resources which span biological scales from molecules to organisms to ecosystems are **energy and information**, as defined above. Our proposal is based on the premise that the exchange of energy, mass, and information at any given scale is what constitutes a “biological entity” or “biological unit”. At each biological scale, we offer an example of the form that energy and information would take at that level. We further identified examples of “energy conductance”, specifically defining one or several factors which dictate the conductance of energy flow, and identified “storage” examples by describing the mechanisms behind the storage and use of energy at each biological scale.

An example application of this framework of scales and resource types is given in Table 1 (for the case of systems related to animals with a nervous system) and Table 2 (for the case of systems related to photosynthetic primary producers). In both cases, at the molecular level, energy is exchanged in at its most basic biological form – ATP. More specifically, we can define energy at the molecular level as the biochemical energy which is embodied in the ATP molecule itself. Likewise, in both cases, the largest scale (ecosystem) provides the source of that energy from sunlight originating in the center of the solar system. Thus, both examples follow an arc that starts at ATP and ends at sunlight. The two examples diverge in the specific interactions at intermediate scales, but at all scales we can define the important players in terms of our four common resource types.

**Table 1. An example focusing on the nervous system of organisms with a brain.**

<b>Molecular Level (ATP)</b>	<p><b>Energy</b> – Biochemical energy that's embodied in the ATP molecule</p> <p><b>Conductance</b> – Relates to factors that dictate the molecular proton gradient</p> <p><b>Storage</b> – “Molecular spring”; covalent bonds of phosphate that are highly unstable. Accumulation of ATP synthase complexes.</p> <p><b>Information</b> – There is a conduit of information upstream from ATP in the sense that ATP biochemistry is a response to the intracellular environment. Similarly, there is a source of information downstream in the sense that ATP facilitates/constrains the cellular processes to which it provides energy.</p>
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<b>Cell Level</b>	<p><b>Energy</b> – Rate of neural processing</p> <p><b>Conductance</b> – Across membrane flux; electrochemical gradients necessary for the formation of action potentials. Membrane conductance to ATP. The availability of limiting reactants.</p> <p><b>Storage</b> – Mitochondria are a vector for the storage of biochemical energy through ATP.</p> <p><b>Information</b> – Spike rates; activation frequencies</p>
<b>Organ/Tissue Level</b>	<p><b>Energy</b> – E.g. Brain scale: The biochemical energy brought into the brain (via chemical bonds in macromolecules) through the circulatory system and also the processes that “drain” the brain.</p> <p><b>Conductance</b> – Dynamics of the circulatory system.</p> <p><b>Storage</b> – Lipid and/or carbohydrate in the form of glycogen stores.</p> <p><b>Information</b> – There are two broad categories of information at this level: sensory input and stored memory of past inputs. These sources of information are integrated in the cortex to form new information generated to predict an organism’s reality.</p>
<b>Organismal Level</b>	<p><b>Energy</b> – Energy is food and water, oxygen, micro and macro nutrients.</p> <p><b>Conductance</b> – Rate of food and water intake</p> <p><b>Storage</b> – Internal stores: Fat and carbohydrates, potentially in conjunction with external sources (E.g. ants can store food in their bodies for other individuals, which represent extended phenotypes).</p> <p><b>Information</b> – Environmental cues and biological cues (both provide information), along with the potential of signals that have evolved to convey information between individuals (E.g. worker bees use visual cues to locate flowers and use special dances to send information about the direction and distance of the nectar source to other individuals).</p>
<b>Community Level</b>	<p><b>Energy</b> – Food; prey and parasite densities as dictated by the structure of a food web.</p> <p><b>Conductance</b> – Movement of organisms in the food web.</p> <p><b>Storage</b> – Prey, as characterized by the population density. <b>Information</b> – Any factors that cannot be described at the individual level but only at the population level (i.e. factors that impact other entities), such as spatial distributions and demographic properties (E.g. The relative density of prey will affect the foraging habits of predators)</p>

<b>Ecosystem Level</b>	<p><b>Energy</b> – Sunlight and biogeochemical cycling (analogous to the circulatory system in the body)</p> <p><b>Conductance</b> – Atmospheric permeability to sunlight and the flux of materials through the ecosystem. Turnover of organic material.</p> <p><b>Storage</b> – Pools of organic material.</p> <p><b>Information</b> – Spatial and temporal distributions of biological and non-biological materials as they impact the functioning of the ecosystem.</p>
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**Table 2. An example using a photosynthetic organism.**

<b>Molecular level</b> (ATP and NADPH)	<p><b>Energy</b> – Contained in molecular spring and high electron orbitals</p> <p><b>Conductance</b> – Linear electron flow limits and pH gradients</p> <p><b>Storage</b> – “Molecular spring”; covalent bonds of phosphate that are highly unstable. Accumulation of ATP synthase complexes</p> <p><b>Information</b> – Acclimation of redox state and proton gradient.</p>
<b>Cell Level</b> (Mesophyll)	<p><b>Energy</b> – From sunlight</p> <p><b>Conductance</b> – Membrane properties that facilitate CO<sub>2</sub> flux</p> <p><b>Storage</b> – Mitochondria are a vector for the storage of biochemical energy through ATP</p> <p><b>Information</b> – Acclimation of the starch pool and time of day</p>
<b>Organ/Tissue Level</b> (in Leaf)	<p><b>Energy</b> – Sum of nutrients, water, sugars</p> <p><b>Conductance</b> – Stomatal/guard cell opening</p> <p><b>Storage</b> – Leaves store their energy in the form of complex carbohydrates such as starch</p> <p><b>Information</b> – Acclimation to light quality and quantity; state of phytochromes.</p>
<b>Organism Level</b> (Plant)	<p><b>Energy</b> – Available in soil and atmosphere gases, liquids.</p> <p><b>Conductance</b> – Xylem and phloem properties.</p> <p><b>Storage</b> – In addition to starch, which can be broken down to form glucose, ATP and NADPH molecules; plants also store glucose in the form of cellulose. Cellulose makes the stem and trunks strong.</p>

	<b>Information</b> – Acclimation allocation to photosynthesizing (leaves and stems) or gathering organs (roots and stems).
<b>Community Level</b>	<b>Energy</b> – Available through sunlight which drives production of energy rich compounds during photosynthesis. <b>Conductance</b> – Movement of competitors, symbionts, and predators. <b>Storage</b> – Population density of plants, symbionts and predators. <b>Information</b> – Acclimation to weather, red to far-red light ratio, and soil-water and nutrient levels.
<b>Ecosystem Level</b>	<b>Energy</b> – Totality of sugars, nutrients, and water. <b>Conductance</b> – Atmospheric permeability to sunlight and the flux of materials through the ecosystem. Turnover of organic material. <b>Storage</b> – Pool of organic material. <b>Information</b> – Spatial and temporal distribution of biological and non-biological materials as it impacts the functioning of the ecosystem; acclimation to weather.

## **GOAL: UNIFYING LIFE SCIENCES UNDER RESOURCE LIMITATION**

**The potential impact** of this vision document is that the use of *resource limitations* across *biological scales* will force us to educate students at a much broader scale. Current approaches to mapping genotypes to phenotypes recognize that the environment plays a critical role, but a general understanding of the limiting energetics of phenotypic expression have not been formulated. Incorporating energetics into phenotyping will better facilitate multi-scale connections from genomes and their resulting phenomes to the ecosystems they are embedded within. It also generates a theoretical approach to scale invariance of resource limitations with testable quantitative hypotheses. This is significant because linking climate change, for example, to resource limitations shall provide a robust framework to deal with a complex biological crisis brought about by global warming. Furthermore, by re-conceptualizing biological systems in terms of similarities and differences across scales, a new avenue of scientific discourse with the public will be opened that may reduce the difficulty in communicating topics such as the difference between weather and climate (i.e., differences that are related to understanding scale).

**Relationship to existing approaches:** Several general fields have already been developed that directly relate to this vision paper. Two in particular are the Metabolic Theory of Ecology (MTE; Gillooly et al. 2001; Brown et al. 2004) and network theory.

*Metabolic Theory of Ecology* explicitly addresses how metabolism (and therefore energy usage) scales across levels of organization from individuals to ecosystems. Moreover, MTE considers constraints imposed by body size, temperature and stoichiometry on metabolic rates. The theory is potentially important in part because global patterns such as species diversity trends along latitudinal or altitudinal gradients may fundamentally result from mass- and temperature-dependent metabolic functions. If so, our current understanding of global-scale patterns such as diversity trends will have to be rewritten. This is important in our basic concepts of ecological principles, but perhaps more importantly, this is crucial to our understanding of ecological consequences of climate change. Nonetheless, while the theory has been shown to fit several data sets (e.g. Bailly et al. 2014; O'Connor & Bernhardt 2018), there is some debate about the fit to other data sets (e.g. Hatton et al. 2019) and whether the theory covers both autotrophic and heterotrophic organisms (Reich et al. 2006). However, the problem with some of these tests is that the data sets can be incomplete or based on non-optimal experimental methodology. Hatton et al. (2019) for example uses basal metabolic rates and maximum reproductive growth rates derived from captive animals. As the authors themselves suggest, these estimates of true metabolic rates and growth rates are not ideal. We call for a more robust investigation of field-based measures that will give us a much better understanding of scale-independent processes. Moreover, our approach calls for extending the basis of the MTE down to molecular and cellular processes.

Addressing the hierarchy of life from the joint perspective of energy and information offers an important synergy between these two approaches. The MTE offers a unique insight into certain scale-invariant properties. However, metabolism (and more generally energy) is an incomplete description of biological systems. The value to this incompleteness is that metabolic processes are clearly understood. The downside of MTE is that it does not offer an understanding of the relative organization of life. This is where the added dimension of information helps us address life in a substantially broader and potentially more robust way. In fact, information (especially relative to Shannon and Weaver's [1949] information theoretic approach) has been used in at least at two levels, animal communication (e.g. Hailman 2008; Freeberg & Lucas 2012) and landscape ecology (e.g. Wang & Zhao 2019; Vranken et al. 2015). A synthesis that truly integrates scale invariance of both energy (as addressed in part by the MTE) and information (as addressed in part by Shannon entropy) would offer a powerful scientific approach to the study of life.

*Network analysis* is an important theoretical framework that has been used to address the organization of life at a variety of scales from molecules (e.g. Qin et al. 2020, Li et al. 2019; but see Flint & Ideker 2019) to metacommunities (e.g. Economo & Keitt 2008). One critical property of networks relevant to this analysis is that they can be used to measure the potential flow of information between units (e.g. Franz & Nunn 2017; Nightingale et al. 2015; McGregor & Horn 2015). As with MTE, more needs to be done either to develop network analysis further to accommodate truly scale-dependent network properties, or to develop new, more robust approaches to scale-independent information content. Nonetheless, network analysis offers a starting point in the development of new theoretical frameworks.

## **BARRIERS/OBSTACLES**

Some of the key barriers and obstacles present in achieving the goals are elaborated below. These include scientific, institutional and pedagogical barriers and obstacles.

**Scientific barriers:** There is no defined unit to improve prediction across scales. In addition, the curriculum needed to provide multi-scale examples to motivate these ideas may require significant collaborative investments by biological educators currently working across these biological sub-disciplines. More broadly, the basic concept of scale is not currently emphasized in the education of the general public. This is exemplified by the public's confusion over the difference between weather (short time and small spatial scales) and climate (long time and large spatial scales). Furthermore, educators and policymakers who shape the public's appreciation of scale may themselves lack an appreciation of it. Suggesting that significant effort should be put into re-framing concepts so that they fit within a scale-free vernacular may be negatively received. Ultimately, there will be significant inertia at institutional and sociological levels in education (either in structured educational settings or in self educational settings) that will resist the adoption of these scale-invariant perspectives.

**Institutional Barriers:** A new approach to biology that crosses scales and disciplines must overcome institutional barriers. For biology researchers in an academic setting, the tenure and promotion process at best does not encourage interdisciplinary or transdisciplinary work, and at worst actively discourages such approaches. Similar barriers are likely to exist in non-academic research settings. Besides changing this academic culture, we must redefine measures of success. For instance, many disciplines in biology and the administrators who oversee the promotion of individuals value papers in which the individual is the first or last author. This archaic approach to evaluating leadership and contribution to papers is an active barrier to improving predictive power across biological scales. Moreover, current business models within institutions that house researchers and the funding agencies that support them require that research resources are controlled by Principal Investigators. This limits creativity and nimbleness because a single PI is unlikely to know about all the research resource issues across the collaborating disciplines on such projects. Furthermore, such consolidation of oversight into single individuals causes interdisciplinary projects to be overly administratively burdensome on the individual. Funding agencies could help alleviate this problem by evaluating how they encourage and reward interdisciplinary work in the same manner that facilities or mentoring plans are evaluated for institutions. Finally, these types of collaborations take time to form and effectively work together as well as space to conduct their work.

**Pedagogical Barriers:** There are significant pedagogical barriers to the adoption of a common vernacular to communicate biological problems across scales. In higher education, students studying and researching in these areas are not taught to think in a scale-invariant way. Furthermore, the concept of scale itself is abstract and closely related to mathematical constructs that may interact negatively with mathematical anxiety that is common in biological students. Thus, it is not trivial to imbue an appreciation of scale let alone an appreciation of why scale-invariant thinking is worth the intellectual investment.

## **POTENTIAL SOLUTIONS TO MITIGATE OBSTACLES**

These barriers are not insurmountable. Here, we highlight some potential solutions to overcoming scientific, institutional and pedagogical barriers, which will aid in achieving our goals.

**Solutions to Scientific Barriers:** As our knowledge base and as the importance of a biological view of life expands, the importance for harmonizing the terminology explaining resources and variability across scales becomes a necessity. Clarity of concepts, consistency of nomenclature, and dissemination of data across scales will facilitate effective transdisciplinary communication, education, and ultimately further discovery.

The unifying concept of harnessing of proton gradients across membranes to drive metabolism in the form of energy or ATP molecules is as universally conserved across biological scales as the genetic code that stores information (Lane, 2017a). Such events could have arisen early in evolution and might have played an important role in shaping the view of the origins of life (Lane 2017b). Therefore, employing a thermodynamic, rather than or in complement to a genetic view of life provides an appropriate framework for developing a consistent theoretical foundation of energy conductance and storage as we scale up from molecules and cells to community and the ecosystem. One could argue that life at a local scale could be explained as moving towards a greater degree of organization (seen as a decrease in entropy) driven by an influx of energy facilitated by the conductance properties of its environment. For example, when living cells grow and multiply into tissues and organisms, they convert chemical energy into heat, which is released into the environment. The released heat increases entropy of the environment, compensating for the decrease in entropy inside the individual living entities. Thus, the ecosystems of the world are maintained as distinct pockets of living and non-living communities in which all life forms sustain themselves through energy transformations. Indeed, recent work on improving the predictive understanding of extreme stress on organisms incorporates the concept that cells must maintain their inside different from outside to define life and death (Guadagno et al 2017).

Various energy resources are required to drive the organization process to produce and sustain life across biological scales. In living entities, energy exists at its most basic form, ATP, which must be broken down to release energy, thus driving the biochemical processes that are favorable across all biological scales. At a complex level, organisms within their communities consume a variety of resources made of carbohydrates and fats along with oxygen to keep themselves alive. At a micro-organismal level, resource availability is variable and potentially rich, ranging from minerals to oxygen. Plants can directly capture sunlight as their main resource and incorporate it for sustaining life. In deep sea vents, besides carbon, there are other chemical elements essential for sustaining life. For example, sulfur metabolism as a fuel resource by microorganisms date the history of metabolism back to 3.5 billion years (Sim et al., 2019). In a most fascinating study published recently (Gleizer et al., 2019), scientists have shown that varying carbon resource pathways by introducing mutations, allows the bacteria to convert CO<sub>2</sub> into sugars for generating the energy source, ATP. By introducing resource variability, a fundamental change in cellular metabolism was observed, which set the stage for the evolution of the microorganism over time.

**Network science:** One way of measuring nutrient resource variability and its impact on exchange of energy and information within cells, to between individuals or populations, is by creating networks. Network science provides a comprehensive toolset for exploring different aspects of biological interactions in biological systems (Gosak et al., 2018). From a thermodynamic perspective, it will be useful to explain the molecular interactions between different resources of energetics, conductance and storage as interconnected networks within a cell. However, we must be cautious about using just one simple network. For example, as a biological entity scales up into an organ (for example the brain), one must expand the fundamental energy network to include architectural and functional properties of the brain as additional network modules, and to study how information, an important resource, is relayed during biological interactions. Thus, as one moves across biological scales, the fundamental energy network along with the organ network could benefit from a third layer of network, which could process the information from the brain and memory, into a prediction of the phenotypic reality (see Table 1). By iteratively adding separate modules of networks to the fundamental energy network, one could come to a comprehensive understanding of the how the two principal resources - energy and information - impact community and the ecosystem functionality as the living entities sustain life across different biological scales.

**Resource-limitation Theories:** Energy and information, the two principal resources, provide a basis for linking fundamental principles of engineering, physics, chemistry, and biology across individual molecules, organisms and ecosystems (Fig. 1). Metabolism is the biological processing of energy transformation that relays information by regulating the rate of nutrient uptake from the immediate environment. Besides the two principal resources, mass and temperature could also play a significant role in affecting the metabolic rate at the molecular, cellular, tissue, organismal, community and ecosystem scales. Overall the metabolic rate sets the pace of life by determining the rates of almost all biological activities across the six primary biological scales (Fig. 1; Brown et al. 2004).

**Funding:** Funding such collaborative projects will allow scientists from multiple disciplines to link metabolism not only at cellular level, but also at the ecological and evolutionary level for sustaining life, thereby opening new areas of research for understanding the consequences of dealing with varying resources across scales.

**Solutions to institutional barriers:** Academia needs to be systematically reorganized in order to advance toward this vision of collaborative, interdisciplinary research on scale-invariant properties of life. First, funding agencies may establish topic-oriented programs to promote collaboration between research groups that cover scale-invariant processes across different scales. In addition, to create a dynamic environment for interdisciplinary collaborations, supporting institutes should provide time and space for collaborative activities. Moreover, interdisciplinary research experience should play a more important role in policies and evaluation procedures across funding agencies, journals, as well as tenure and promotion processes.

**Solutions to Pedagogical barriers:** Vertical integration of diverse pedagogical solutions from K-12 levels to undergraduate and graduate schools represents one promising solution to prepare

future generations of life scientists and citizens. A pyramid structure with a broad and solid educational foundation at the K-12 levels is essential to supporting and cultivating an atmosphere for intellectual exploration and technological innovation that hopefully culminates in scientific discoveries in dealing with varying resources across different life scales. Practically, this will require extensive communication and consultation in order to achieve harmonization of state K-12 educational standards and life science curricula at higher education institutions.

## **FUTURE IMPACTS AND NEW DIRECTIONS THAT WILL BE ENABLED**

The reintegrating of biological investigation as outlined here will impact several dimensions of the scientific enterprise.

**Education:** Expanding the integration of disciplines across scales will require a change in the educational system. We will continue to require in-depth scientific inquiry at each scale. However, we will need to educate a subset of scientists who are capable of integrating information across scales. An important ancillary consequence of this additional educational level is the facilitation of cross-talk across disciplines.

**Scientific Inquiry:** Expanding the integration of disciplines across scales should result in new approaches within disciplines thereby increasing our ability to make predictions about the processes of life from phenomes through ecosystems.

**Applied Science:** As an example, climate change will unequivocally affect life at all scales. An integrated framework of scientific inquiry will provide a robust way to address the consequences of this ongoing problem. Indeed, the scope of the impact of climate change across scales is best addressed using a scientific framework that integrates scales.

**Theoretical models:** Paradigm shifts often result from adapting theories generated in some fields and integrating them into other fields where they provide deeper insight into biological phenomena. The reintegration of biological investigation is designed to fast-track this integration by incentivizing cross talk between disciplines.

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