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A Minimal Framework for Describing Living Systems: A Multi-Dimensional View of Life Across Scales

Kelsey Caetano-Anollés ^{*}, Brent Ewers[†], Shilpa Iyer[‡], Jeffrey R. Lucas[§], Theodore P. Pavlic [¶],
Andre P. Seale^{||} and Yu Zeng [#]

^{*}Callout Biotech, Albuquerque, NM 87111, USA; [†]Department of Botany and Program in Ecology, University of Wyoming, Laramie, WY 82071, USA; [‡]Department of Biological Sciences, J. William Fulbright College of Arts and Sciences, University of Arkansas, Fayetteville, AR 72701, USA; [§]Department of Biological Sciences, Purdue University, West Lafayette, IN 47907, USA; [¶]School of Computing, Informatics, and Decision Systems Engineering / School of Sustainability / School of Life Sciences, Arizona State University, Tempe, AZ 85287, USA; ^{||}Department of Human Nutrition, Food and Animal Sciences, University of Hawai'i at Mānoa, 1955 East-West Road, Honolulu, HI 96822, USA; [#]Schmid College of Science and Technology, Chapman University, Orange, CA 92866, USA

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¹E-mail: kelseyca@gmail.com

Synopsis The almost limitless complexity of biology has led to two general approaches to understanding biological phenomena. One approach is dominated by reductionism in which high-level phenomena of whole systems are viewed as emerging from relatively simple and generally understood interactions at a substantially lower level. Although this approach is theoretically general, it can become intractable in practice when attempting to simultaneously explain a wide range of systems. A second approach is for specialists to investigate biological phenomena within one of many different hierarchical levels of description that are separated to decouple from concerns at other levels. Although this approach reduces the explanatory burden on specialists that operate within each level, it also reduces integration from insights gained at other levels. Thus, as beneficial as these approaches have been, they limit the scope and integration of knowledge across scales of biological organization to the detriment of a truly synoptic view of life. The challenge is to find a theoretical and experimental framework that facilitates a broader understanding of the hierarchy of life—providing permeability for the exchange of ideas among disciplinary specialists without discounting the peculiarities that have come to define those disciplines. For this purpose, coarse-grained, scale-invariant properties, and resources need to be identified that describe the characteristic features of a living system at all spatiotemporal scales. The approach will be aided by a common vernacular that underscores the realities of biological connections across a wide range of scales. Therefore, in this vision paper, we propose a conceptual approach based on four identified resources—energy, conductance, storage, and information (ECSI)—to reintegrate biological studies with the aim of unifying life sciences under resource limitations. We argue that no functional description of a living system is complete without accounting for at least all four of these resources. Thus, making these resources explicit will help to identify commonalities to aid in transdisciplinary discourse as well as opportunities for integrating among the differently scoped areas of specialized inquiry. The proposed conceptual framework for living systems should be valid across all scales and may uncover potential limitations of existing hypotheses and help researchers develop new hypotheses addressing fundamental processes of life without having to resort to reductionism.

Introduction

Although biology has benefited from a high degree of specialization into several sub-disciplines, this compartmentalization now presents challenges to inte-

grating across scales of inquiry. Within biology, two researchers working at a similar scale (e.g., animal physiology) can agree on a common set of research motivations despite working on fundamentally different model

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organisms. However, qualitatively different motivations might exist between researchers working at scales most relevant to cellular and molecular questions compared to researchers working on ecological or evolutionary questions. Although biologists share a common interest in understanding the fundamentals of living systems, there are significant barriers to meaningful discourse among practitioners who work at different spatiotemporal scales. Furthermore, a lack of integration across scales creates a silo mentality within each compartmentalized discipline as researchers working at one scale are unable to provide conceptualizations that are important to researchers working at other scales. We believe biologists will broadly benefit from a common conceptual framework that allows for fundamental problems at all scales to be expressed in a widely understood vernacular that emphasizes the scale-independence of important biological phenomena. Moreover, we expect that our conceptual framework will help break down silos while also allowing tools, data, and models from particular disciplines to be better communicated to other disciplines.

To form this language, it is necessary to make explicit a minimal set of dimensions that can be used at any spatiotemporal scale to describe the salient features of a living system (Fig. 1). Even if there are no rules of life that apply uniformly across all scales, we assert that there should be a set of resources that are necessary to describe all living processes across any scale. Once such common resources are identified, the search for scale-invariant rules of life (or even rigorous explanations for the necessity of scale variance) will be simplified because descriptions of processes at different scales will be expressed using comparable language. Furthermore, theories that have been influential in studies at one scale can more easily generate hypotheses that can be tested in the search for such common rules of life at other scales. The resource types relevant at all scales could further aid theoreticians and empiricists alike in ensuring that their study systems have explicitly accounted for potentially critical drivers of the biological phenomena under study and thus provides theoretical context needed to determine the scale of measurements.

In this vision paper, we identify four generic resources—energy, conductance, storage, and information (ECSI; Fig. 1A)—that are necessary (although possibly not sufficient) to describe living systems across all spatiotemporal scales (Fig. 1C). A conceptual framework for living systems that applies across all scales promotes re-integration of biology. Furthermore, such a framework highlights the limitations of some hypotheses and potentially helps to identify entirely new hypotheses that will

better answer fundamental questions about life's processes.

Scale-invariant ECSI framework: Energy, conductance, storage, and information

The field of systems biology emphasizes that important biological phenomena occur as a result of complex interactions among biological entities. The notion of a biological system suggests that all phenomena can be explained in part by the interaction of components internal to the system (endogenous causes) and in part by external drivers that must be taken as independent inputs (exogenous causes). Defining the boundary of a system—identifying which biological entities and interactions are to be explicitly accounted for and which ones are to be lumped into inputs and parameters whose provenance lies external to the system—is thus a critical component of modeling in systems biology. Although systems thinking is made more explicit in systems biology, the notion of choosing focal entities is common to all fields of biological study. We propose a framework for all biological research that guides both the choice of system boundaries and the dissemination of those choices to researchers in other disciplines.

The framework we develop is built upon the notion of four generic resource types—energy, conductance, storage, and information (ECSI)—as depicted in Figs. 1A and B. We employ these terms according to their distinctively established disciplines as follows.

Energy is defined as Gibbs free energy or free enthalpy (Greiner et al. 1995). According to Gibbs, free energy is the total energy of a system that is available to perform useful work. Energy is the principal causal agent in evolution—gaining access to this limited resource is critical for the survival of living organisms. Thus, living systems are both a shadow of the availability of the flow of energy as well as filters that disrupt the course of that flow, and this interplay fundamentally shapes the historical pattern of life (Eldredge et al. 2016), going back to even before the origins of life. At the highest levels, free energy is sourced from the sun, whose progress toward an eventually cool equilibrium has the side effect of temporarily reversing a similar progression on earth. Furthermore, the availability of free energy from the sun has allowed for out-of-equilibrium metabolic activity that has, over time, generated primary producers that themselves reach toward and follow the path of the sun. With the existence of these out-of-equilibrium primary producers, primary consumers that could hold themselves out of equilibrium could evolve without direct access to the sun, and then secondary consumers could exist even farther removed from the ultimate source of free energy. The

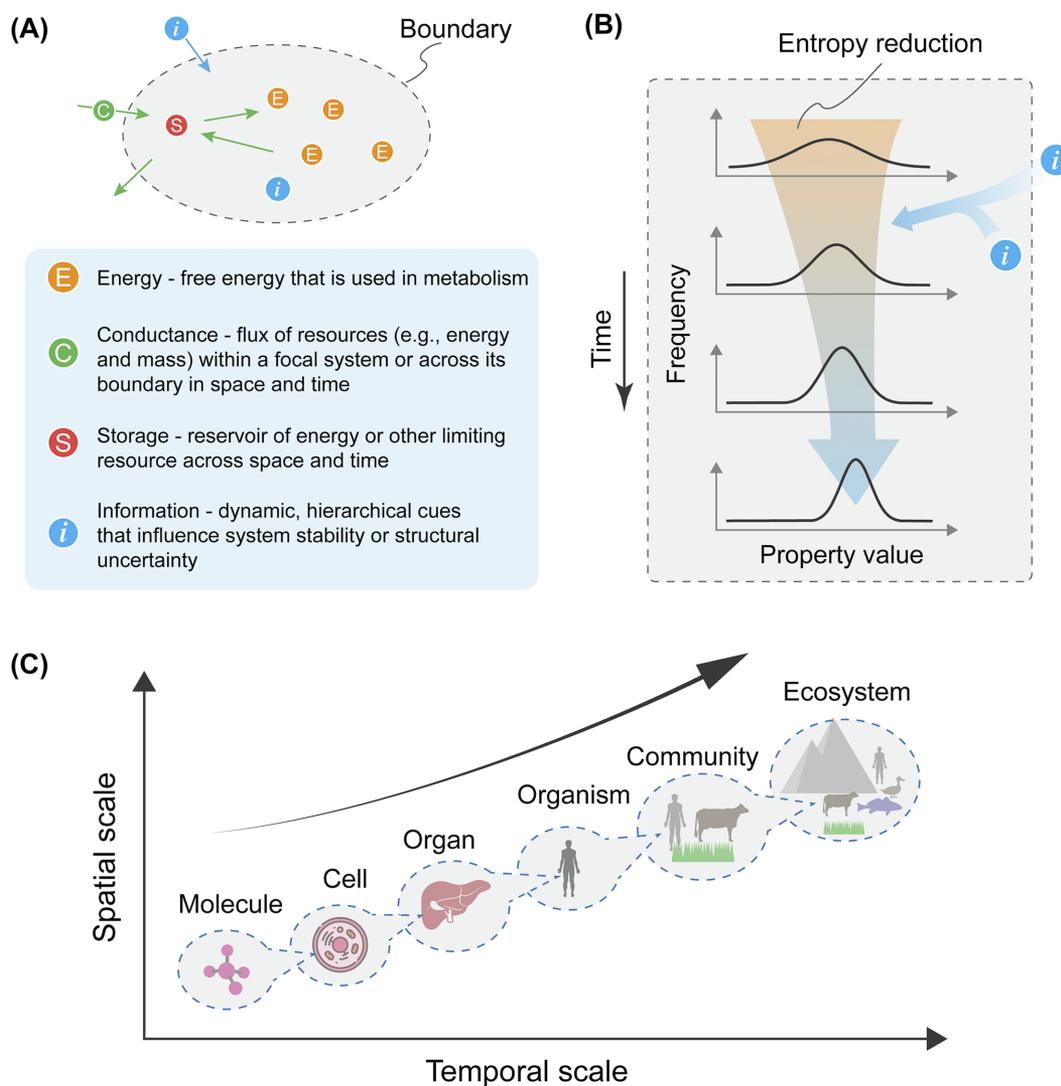


Fig. 1 Overview of ECSI Framework. **(A)** Schematic diagram for the relationship of four basic ECSI components (defined in gray box) for a generic system. Any description of a living system must account for all four resources. Systems powered by free energy (E) must cope with constraints on energy and matter availability (C), making use of storage (S) to both buffer against severe rate constraints and to provide memory (I) to better anticipate regularities within the system as a whole. **(B)** Information component of a living system. Dynamical cues are used by hierarchical control laws in living systems to reduce uncertainty (as measured by entropy in diagram). Entropy-reducing information is stored within the system and injected from outside of the system. **(C)** A conceptual view of life that crosses time, space, and scales from molecules to ecosystems, where the ECSI components depicted in the generic system in (A) occur at each scale.

history of living systems both follows and re-distributes free energy, and (free) energy is a resource that naturally permeates all scales of life. By ensuring that it is accounted for, there are immediate opportunities to compare and contrast the role of free energy at all scales of investigation.

Conductance is the ability of a system to facilitate flow or fluctuations (flux) of energy or matter. As described above, energy is a significant limiting resource of life, and the rate that energy can be delivered constrains the activity of living systems. However, living systems are physically embodied and thus are similarly limited by the availability of matter over time.

Consequently, ecosystems are characterized by fluxes of material and energy. Conductance can be exemplified by gases moving across a membrane at small scales or by the movement of organisms across a landscape at large scales—both which share the characteristic of not being instantaneous. From a biogeochemical perspective, the interplay of rate-limited fluxes is the basis of all life on the planet (Eldredge et al. 2016). An explanation can be made through an example, such as conductance of blood and nutrients as function of the heart. In cardiac muscles, mitochondria, which are the energy powerhouse of the cell, occupy about 40% of the total volume (Page and McCallister 1973) and provide about

90% of the adenosine triphosphate (ATP) required to perform the function of the heart (i.e., pumping blood). To exist, the heart depends on the efficient organization of the body (Table 1), which ensures rapid distribution of matter carried in the blood through arteries and veins as well as sufficiently fast removal of toxic matter in the liver (Fig. 2C and D), among other activities. The free energy stored in ATP and the material within the blood cannot sustain life without also being able to be made available at a sufficient rate. Thus, conductance is another form of resource that can be identified at all levels of life.

Storage is complementary to conductance; it allows for surpluses of material and energy at one time to be used later when otherwise unavailable from external sources. Living organisms use various molecules to store free energy. Many store different sugars, while others store lipids (Table 1). Most plants use photosynthesis to convert free energy from sunlight and carbon dioxide from the air to produce carbohydrates, which are then stored to allow for that free energy to be used even when sunlight is not available (Fig. 3C and D). Generally, free energy is stored in the bonds of the reactants and products of a reaction. One way this free energy is captured in living entities across scales is by producing ATP from adenosine diphosphate (ADP) by the addition of an inorganic phosphate group. The bonds between the phosphate groups in ATP are high-energy bonds because their hydrolysis is accompanied by a relatively large decrease in free energy (Alberts et al. 2014). Therefore, the high-energy bonds of ATP play a central role in metabolism (Figs. 2F, 3D, and Table 1) by serving as usable storage of free energy.

As illustrated in Fig. 1A, storage also represents the accumulation of other material fluxes through time and space. For example, along with energetic stores (e.g., stored energy derived from carbohydrates and fats), organisms may have to accumulate and store other macronutrients (e.g., proteins and amino acids) or materials (e.g., water) that similarly limit the dynamic function of the organism. Furthermore, organisms may be provided with an ever-declining store of some resources at birth (e.g., eggs). The state of the stores of these different currencies (e.g., starvation or thirst) has a direct influence on the behaviors of organisms—such as when and how to forage and when to engage in competing activities, such as reproduction. Thus, just as the rate that resources can be made available (conductance) plays a role at every biological scale, so do low-conductance mitigation strategies afforded by storage.

Information is taken as an index of potential variation in a system that can organize that system in a given environment (Dusenbery 1992). We follow

Stonier's (1990) view where information by itself is a resource that can be stored in energetic and material configurations at any level of organization. As Stonier (1990) states, "The non-random distribution of atoms and molecules in living systems, that is, the intricate organization 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" (Stonier 1990, 13). A critical aspect of the concept of information is that it is part of a dynamic process that causes a reduction in uncertainty in a system (see Appendix); for example, the position of the sun in the sky reduces the uncertainty about when it will set in the near future, and a circadian rhythm that is synchronized to the photoperiod reduces the uncertainty about when the sun will rise before the upcoming morning. Thus, like energy, information can be viewed as a fundamental resource that can be found in the external environment (e.g., position of the sun) or stored within an organism (e.g., the configuration of the circadian clock).

Although information is itself a fundamental resource, it can also serve to enact contingencies related to other ECSI resources. For example, whereas storage helps to mitigate the effects of low conductance, information can help to regulate the rate of activity to prevent the depletion of stored resources before they become externally available again. A starving animal is replete with information that it resides in a poor environment, and so it should exploit any food patches it finds for as long as possible to increase its stores as much as possible. In contrast, an animal that regularly encounters rich food patches and thus is far from starving will benefit from spending more time searching for new patches with a high rate of return than depleting old patches (Stephens and Krebs 1986). The information about the habitat richness is effectively information about the conductance of energy and can be used to determine how to use and maintain storage. Thus, in this example, energy enables life, and all living activity is constrained by the conductance of energy and matter, but storage can reduce dependence on external sources of energy and matter so long as information is used to regulate those stores over time.

As summarized in Fig. 1C, we focus our discussion of ECSI primarily on six biological scales 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). These scales do not necessarily represent every biological scale in our universe, but rather represent a general distribution of biological entities and processes in life as we commonly understand them. As we discuss below,

Table 1 An example of ECSI applied to ecosystems across scales

A: Ecosystem	<p>Energy: Energy flow from sunlight is taken up by plants (primary producers) via photosynthesis and this distribution of energy down the food web by primary and secondary consumers fuels life.</p> <p>Conductance: Conductance is the measurement of the energy flowing (flux) through a system to sustain life. This energy is acquired from the environment (non-equilibrium thermodynamics) and is the reason why organisms live-to eat and breathe.</p> <p>Storage: The energy storage are groups of important biological molecules such as carbon and hydrogen along with oxygen and nitrogen as the primary gases. Their chemical bonding properties provide the diversity that exists in all life forms.</p> <p>Information: Complex structures are generated and maintained through energy flux. The energy from sunlight flowing through the biological molecules provides the vital calories for growth, survival, and reproduction of complex structures which embody information that is transferred from one generation to the next.</p>
B: Community	<p>Energy: By consuming primary producers (plants use sunlight) and hunting primary (e.g., small fish) and secondary consumers (e.g., ducks), energy moves via different population food web groups at the community level.</p> <p>Conductance: Food webs show how energy flux moves between organisms throughout a community. This has implications for maintaining different population densities as they continue to grow.</p> <p>Storage: Population density of primary and secondary consumers, and primary producers.</p> <p>Information: Efficient availability of energy to do useful work is at the heart of many environmental issues. Factors that impact the availability of energy and matter impact the survival of many organisms within the ecosystem, thus affecting the distribution and abundance of organisms at the community level.</p>
C: Organism	<p>Energy: At an organismal level, many organ systems work together to perform tasks required by the independent organism. The digestive system works with other organs in the human body to absorb water and break down food to proteins, fats, carbohydrates, and nutrients leading to energy conductance within the entire organism.</p> <p>Conductance: The human body is composed of ~60% water. Water is the medium for all movement within the body. Water balances acids, moves nutrients, metabolites into cells and contains electrolytes which enable the flux of electrical signals to generate energy through the body and allow the body to work.</p> <p>Storage: Food is stored in the form of proteins, lipids, and carbohydrates, in conjunction with metabolites and electrolytes as nutrients.</p> <p>Information: Environmental and the endocrine systems (both provide information) along with potential hormones trigger signaling pathways throughout the human body. These signals can be used to communicate with other individuals and examine the informational content of the community-wide communication networks. For example, one can understand the transmission rate of the coronavirus (COVID-19) and the number of days being contagious; leading to self-isolation of infected individuals for those many days at an organismal level.</p>
D: Organ	<p>Energy: Every organ is made up of two or more tissues that work together to perform a specific task. The four principal tissue types are epithelial, connective, muscle, and nervous tissue. The nervous tissue primarily uses glucose and when this nutrient is scarce uses ketones for energy. Muscle tissue uses fatty acids, glucose, and amino acids as energy sources. Connective tissues such as adipose tissue, use fatty acids and glucose for energy, whereas red blood cells require glucose for energy to convert to lactate. Epithelial cells lining the inner organs are involved in absorption or secretion. For example, the hepatocytes present in the organ liver are essential for providing energy to the nervous, muscle and connective tissues in peripheral organs.</p> <p>Conductance: The liver contains 13% of the body's blood supply. Conductance in the form of oxygenated blood flowing in from the hepatic artery and nutrient rich blood flowing in from the hepatic portal vein regulates the osmolarity and electrolyte composition of the blood. A variety of sensory receptors in the hepatic artery are sensitive to changes in the nutrient rich blood glucose concentrations in the hepatic portal vein. The portal vein contains metabolic receptors whose function is to detoxify and maintain a stable pool of circulating metabolic fuels in the blood plasma. Together the sensory and metabolic receptors in the liver work with different tissues to trigger feeding behavior and gastric acid secretion. Energy is thus moved along different primary and secondary consumers at an organ level.</p> <p>Storage: Fatty acids, vitamins, minerals, proteins, and carbohydrates (glycogen) are stored in the liver.</p> <p>Information: There are two broad categories of information at this level: sensory and stored information because of memory due to past inputs. These sources of information are integrated into the cortex to form new information. For example, the location of sensory and stored receptors controlling feeding and gastric acid input has been assigned to the brain. However, metabolic receptors in the liver are activated by decreases in glucose receptors in the brain; leading to oxidation of metabolic fuels in the liver.</p>
E: Cell	<p>Energy: A cell is the basic unit of life and is made of different molecules. As shown in Fig 2C, the human body is made up of 30 trillion cells with over 200 different cellular types specialized to carry out particular functions with the body. For example, muscle cells contract to perform work while red blood cells carry oxygen. The cells are made up of cell membranes to enclose the cytoplasm and cellular organelles. The subcellular organelle called mitochondria uses molecular oxygen to release free energy from carbohydrates, proteins, and fat within the cell, to synthesize ATP for the host cell. The process is called cellular respiration.</p> <p>Conductance: Within the cell, a series of redox reactions produce three molecules of electron carriers' nicotinamide adenine dinucleotide (NAD⁺ in its oxidized form) and one molecule of flavin adenine dinucleotide (FAD in its oxidized form), which enter the mitochondrial inner membrane to shuttle electrons along the electron transport chain and pump protons across membranes to produce an electrochemical proton gradient (equivalent to 0.2 volts of electric potential). Thus, energy of the proton potential is coupled to ATP synthesis catalyzed by ATP synthase embedded in the membrane. The pyrophosphate bond energy in ATP is then transferred by diffusion to the rest of the cell energy flowing towards a variety of metabolic functions, protein polymerizations, and ion transport within the cell.</p>

Table 1 Continued

F: Molecule

Storage: Within a cell potential energy is stored as ATP molecules, much like a compressed “molecular spring”. When covalent phosphate bonds that are highly unstable are pulled away or “relaxed” during a chemical reaction, the stored energy is redeemed to perform different types of work by a cell.

Information: The coupling of ATP synthesis to electron transfer and proton gradient pumps provides a conduit of information on cellular response to its local environment within a cell. Once the level of ATP falls it could lead to tissue dysfunction and organ disease leading to disease of the entire organism or individual, which in turn could influence survival patterns within the ecosystem.

Energy: Adenosine-5'-triphosphate (ATP), serves as the main source of free energy in living cells. Adenosine consists of the nitrogenous base adenine and the five-carbon sugar ribose. The three phosphate groups are attached to the ribose sugar. Together, these chemical groups are used to power the majority of the cellular functions requiring energy.

Conductance: Hydrolysis of one of the three phosphoanhydride bonds of ATP, breaks the bond and releases free energy (exergonic reaction) when it transfers a phosphate group to another molecule to form adenosine diphosphate (ADP).

Storage: Each molecule of ATP stores a small quantity of chemical energy in the three phosphate groups called phosphoanhydride bonds.

Information: Polymerization of monomers to form the ester bonds of nucleic acids, glycosidic bonds of polysaccharides, and peptide bonds in proteins is an energy driven process. Polymerization occurs by hydrolysis of ATP to ADP, which transfers the phosphate group to the monomer to drive energetically favorable reactions used in many pathways in the cell. Information for continuous energy flow or conductance is provided by ATP hydrolysis to drive many reactions forward in all living beings from cells all the way to ecosystems (Fig. 1C), thus explaining the maintenance of complexity.

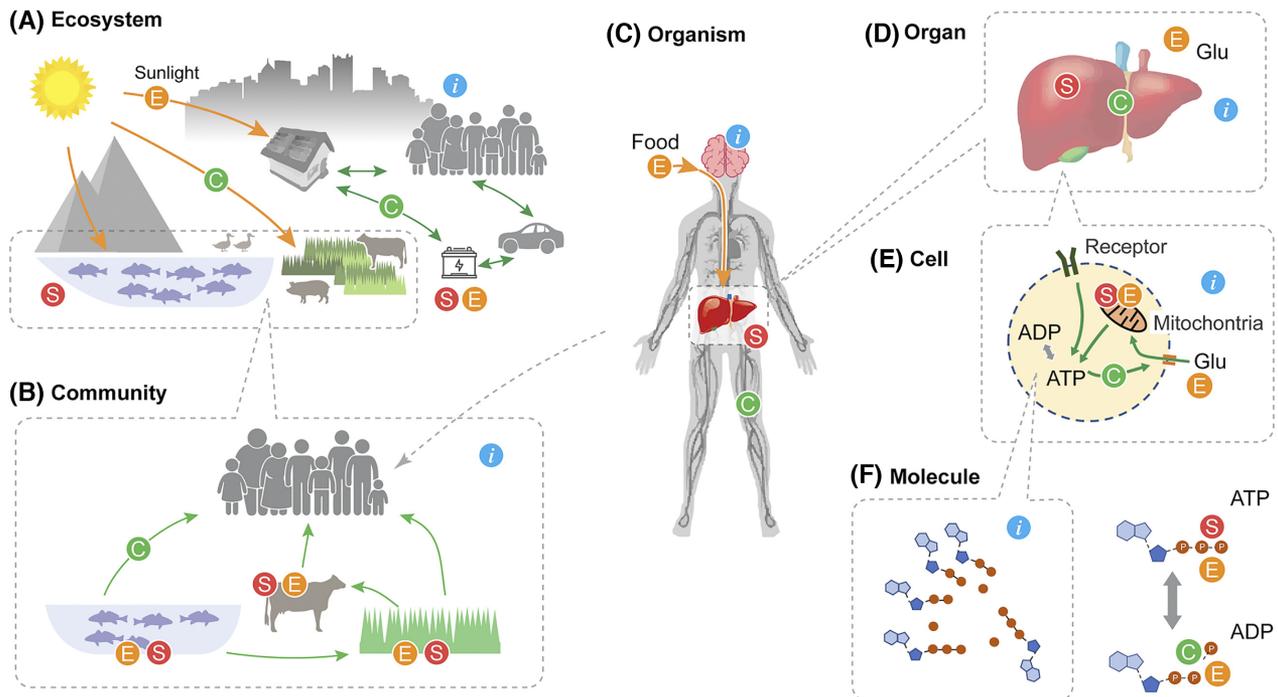


Fig. 2 An example of the use of ECSI at multiple scales across Ecosystems. Abbreviations: Glu—glucose; ATP—adenosine triphosphate; and ADP—adenosine diphosphate. **(A)** At the ecosystem scale, energy (E) fuels all activity that is a product of the biosphere, with excess energy stored (S) in various forms; however, the rate of all activity is ultimately limited by flux constraints (C). Humans build regularly structured societies (I) that control their niche and allow for human civilization to operate anywhere. **(B)** At the community scale, species abundance (S) is necessary for community function, and availability (C) of species in trophic interactions (E) ultimately limits community productivity. Information about scarcity (I) can lead to behavioral changes. **(C)** At the organism level, an animal must move to obtain energy (E) from food, which requires information (I) about potential locations to forage. Motion is triggered by reduction in stored (S) resources, but physiological constraints (C) limit the rate by which nutrients may be transported, ultimately limiting movement. **(D)** At the level of an organ, energy (E) is necessary to operate regulatory feedback loops (I) that respond to changes in input, such as nutrient uptake, as well as the output of stored (S) chemical energy within the organ. Ultimately, the action of the organ is limited by metabolic constraints (C). **(E)** At the level of the cell, energy (E) acquired in the form of glucose is stored (S) as ATP in mitochondria, whose availability limits (C) the ability of the cell to produce proteins that respond appropriately to local cues (I). **(F)** At the level of the molecule, electron transfer (C) permits energy (E) to be stored (S), and the availability of ATP (I) is a cue of the past availability of energy.

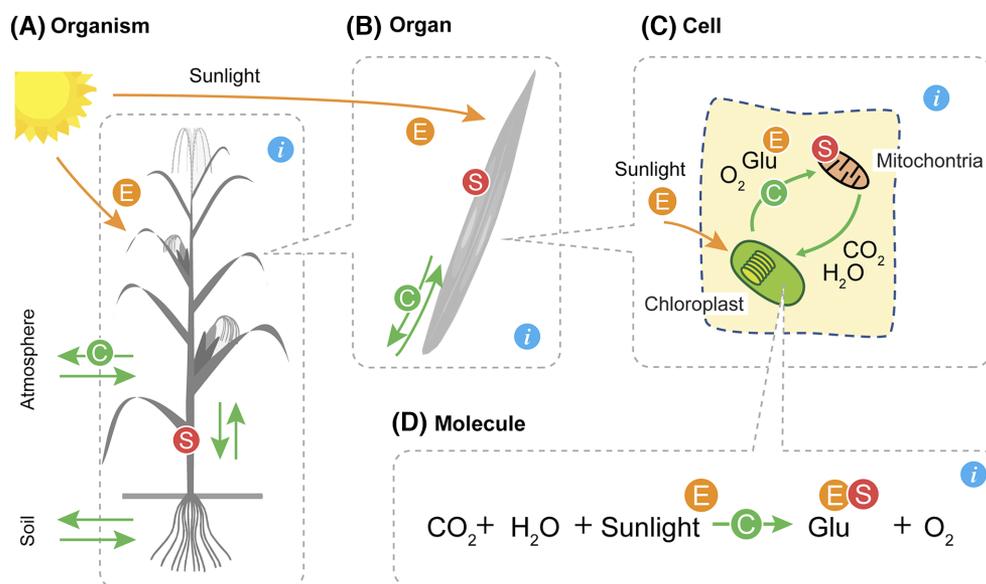


Fig. 3 An example of the use of ECSI at multiple scales within a primary producer. **(A)** At the organismal scale, information (I) about the position of the sun and the direction of gravity drives growth to ensure access to energy (E) from the sun and nutrients from the earth, but uptake of these resources is facilitated by conductance (C), and so resources are stored (S) within the plant to be used when external energy is limiting. **(B)** At the organ scale, energy (S) from the sun is converted into sugars that are stored (S) and transported throughout the plant, but this conversion is only possible if water is available (C). The leaf must respond to cues from the sun (I) to ensure efficient conversion. **(C)** At the cell level, energy (E) from the sun participates in photosynthesis for energy storage (S); however, the respiration activity of the cell is also limited by the availability of stored energy (C). Mechanical stresses in the walled cells of a plant provide information (I) related to growth and development. **(D)** At the molecular level, energy (E) from sunlight is stored within synthesized glucose (S) in a metabolic process that is rate limited (C), and the resulting products of that reaction provide information (I) about the availability of resources.

these four resource concepts (ECSI) allow for discourse and research ideation focusing idiosyncratically within each scale while still providing a framework for understanding characteristic similarities across scales. More fundamentally, the ECSI framework helps to identify four resources that are fundamental to every scale of life and thus helps to promote interdisciplinary engagement across multiple disciplines of biology.

Without attempting to redefine life, the proposed framework is based on the premise that the exchange of energy, mass flow, storage and information at any given scale is what sustains a “biological entity” or “biological unit.” Therefore, life scientists should focus on two fundamental resources (energy and information) as well as those that facilitate their exchange (conductance) or allow them to be accumulated (storage). Without the interactions among these four resources within a given scale, the requirements needed to sustain a stable system may become compromised. Conceptually, one can test this hypothesis by removing or exacerbating one or more of the resources and forecasting the outcome within and across scales. For example, without the capability for *storage*, *energy* would need to be acquired and spent at every instance in time and space to support a given biological entity. Furthermore, in such

a no-storage scenario, instantaneous biological activity would be limited by the conductance of energy transfer (as well as other material resources). Storage capability mitigates the limitations of conductance. However, without information about the amount of energy stored and the likely amount of energy available in the future (due to both energetic availability and conductance limitations), biological activity will be similarly limited as in the no-storage case because these stores could be exhausted without responsive management. It is only through regulatory processes that acquire and respond to information that independent biological activity can be sustained for long durations. Thus, for a complete description of sustained biological activity at any scale, at least all four ECSI resources are necessary. Moreover, there are opportunities to develop fundamental theories of tradeoffs among these four resources. In the example above, increases in conductance or information use can both reduce the reliance on storage. Furthermore, although energy is fundamental in all biological contexts, the other three resources (C, S, and I) can also be applied to matter as well as more complex aggregations of biological material—as in understanding the drivers and consequences of exchange across metapopulations. Even if the ECSI resources and interactions may not

be the only ones that dictate the flow of hypothetical scale-invariant properties of life, they still serve as a foundation by which other hypothesized relationships can be further interrogated.

Making “information” unambiguous in ECSI

Before providing more detailed examples of how ECSI can be applied across scales, we clarify our particular use of “information” within the framework of this vision paper. Of the four ECSI resources, information is likely to be the one resource with different meanings to many life scientists. Unlike “energy” (which is specific enough to not warrant elaboration) and “conductance” and “storage” (which are general enough to cover most meanings simultaneously), “information” can be used to describe several different concepts (McKinney and Yoos 2010, some of which are not addressed here and referenced elsewhere, as by Wallace 2013). Many of these concepts are also related to “cognition” (the processing, storage, and use of information; Shettleworth 2010) in animals with relatively large brains (e.g., Japyassu and Laland 2017). Linking information with cognition further limits the utility of the word for our scale-invariant approach (although see Bechtel and Bich 2021). However, the concept of information has been discussed in a much broader context (e.g., Stonier 1990; Dusenbery 1992; Bawden and Robinson 2020) that makes it highly relevant to our thesis. Therefore, before providing more detailed examples of how the ECSI framework can be applied across scales, we explore our choice of “**information**” as one of the canonical dimensions of life.

Consider the following patterns of information flow in a variety of systems. In each case, we describe a system, an information source, and dynamics that result from the processing of the information. As these examples show, the scale-independence of the concept of “information” is underscored by the use of identical metrics for measuring uncertainty, information flow, and information updating across scales (details on methods for quantifying information are surveyed in the Appendix).

Drosophila larvae develop a segmentation pattern that is critical for their development (e.g., Nüsslein-Volhard and Wieschaus 1980). The segmentation patterns result from a feed-forward flow of information where maternal morphogens drive the expression of four different gap genes, which in turn drive the expression of pair-rule genes. The pair-rule genes define the position of the segments in the developing larva. Petkova et al. (2019) showed that all four gap genes are required to provide the resolution of spatial information necessary for the proper functioning of the pair-rule

genes. Here, the system is the tissue in the developing larva. The information source is the spatiotemporal gradients of morphogens and gene products. In particular, the gradients of gap gene products generated by the cluster of four genes in turn generate a sharply defined, low-variance gradient needed for the proper functioning of the pair-rule genes. If one of the four gap genes is turned off, then the precision of the activity of the pair-rule genes is too low causing a disruption of correct spacing of body segmentation.

The neural representation of signal processing in the peripheral auditory system and brainstem undergoes seasonal retuning, which results in enhanced processing of season- and species-specific vocalizations. This seasonal plasticity enhances information decoding of vocal signals in a number of taxa such as birds (Lucas et al. 2007) and fishes (Sisneros et al. 2004). The system in this example is the auditory system. The information is generated by the vibration of a membrane in the inner ear that is converted to a neural spike train passed to the auditory nerve. Of course, the neural representation of the vocal signal itself is ultimately what is being transcribed into the detection of song as it is processed in various parts of the auditory system from the ear up to the brain. However, that neural representation is season specific—the animals “hear” the exact same song slightly differently in the winter than they do in the spring. This is why we should think of the information as being physiological instead of being encoded in the properties of the physical sound.

Individuals gather sensory information about environmental parameters that reduces uncertainty about fitness-relevant aspects of their environment such as food and predation risk (Dall et al. 2005). The system in this example is clearly the individual and the information is sensory information gathered relative to properties of the food resource or predator population. Populations of animals with complex social systems have more complex communicative systems than animals with less complex social systems (Freeberg et al. 2012). The correlation between social and communicative complexity results from a need for greater levels of information transfer in animals with relatively complex social systems (e.g., Krams et al. 2012). The system in this example is the population of potentially social animals. The information has to do with encoding representations of the “world” in specific vocal signals. The processing of these signals then alters the “world view” of individuals receiving the communicative signals. Note that the information is not in the collection of signals *per se*, but in the specific signals that can be decoded by the receiver in a way that causes the receiver to update its view of the world. If individuals share information relative to many contexts

(e.g., food, territory defense, and predation risk), then they need a more extensive communicative system in order to convey a broader range of information. Note that information in this example is external to the individual but internal to the social group.

Just as an animal collects sensory information about a predator, so do some seeds collect environmental information about rainfall patterns (Donaldson-Matasci et al. 2010). Moreover, shared information processing across species can result in the adaptive masting of seeds in entire plant communities when individuals across a diversity of taxa respond to similar environmental cues (Schauber et al. 2002). The system in this example is the community of masting plant species. The information source is generated by temperature changes. The signal specifically discussed by Schauber et al. (2002) is environmental temperature—masting that resulted from anomalously high temperatures caused by La Nina ocean currents. Thus, the information is the temperature profile detected by the plant community.

Shared information processing is the basis of many examples of mass animal migrations. An example is the massive migration of mammalian grazers in African savannas (McNaughton et al. 1997). In addition, the link between animal movement and the environment can lead to feedback loops that amplify the predictability of the entire ecosystem through a coupling of animal migration patterns and the impact of their nutrient cycling on plant growth. Alteration of a population's or community's environment in a way that increases the viability of those systems is a process called niche construction (Riotte-Lambert and Mattiopoulos 2020). The point here is that information flow can both directly and indirectly impact ecosystem dynamics. This is a complex example because the system of mammalian grazers is nested in the savanna ecosystem. As a result, the information sources in this example are hierarchical. Migrating ungulates use social cues (internal) and environmental cues (external: map sense, temperate, and water cues) to determine when and where they migrate. This obviously occurs at the population and community level; however, niche construction makes this example relevant at the ecosystem level (i.e., communities of organisms coupled with nutrient recycling). Different ungulates use different strategies based on the information from vegetation greening, in some cases surfing the green wave of near optimal forage (Aikens et al. 2020) and in some cases actually creating the green wave (Geremia et al. 2019). Thus, information flow is hierarchical. The grazers use several sources of information to guide their migration. The migration patterns in turn generate feedback dynamics that result in niche construction,

and these feedback dynamics provide information that stabilizes the savanna ecosystem.

One property that is central to our framework is the fact that information is part of a dynamic process that results in a reduction of uncertainty in a system (Fig. 1B; Donaldson-Matasci et al. 2010; Pharoah 2020). This process of uncertainty reduction is as relevant in a signal transduction pathway within a cell membrane (Lean 2014) as it is in niche construction resulting from the massive ungulate migrations in the African savanna (Riotte-Lambert and Mattiopoulos 2020).

Complementing and extending existing theories and tools through the framework of ECSI

Through ECSI, we offer a system-based approach that focuses on the organizational dynamics of natural systems that are intrinsic to life at all levels. Although energy, conductance, storage, and information are critical elements of life at all scales, we do not imply that system dynamics will inevitably be scale-independent, nor do we imply that ECSI represents an exhaustive list of resources. We envision ECSI as a starting point for evaluating both scale-independent and scale-dependent properties of life.

Previous attempts to synthesize the fundamental properties of life across scales have led to useful working theories. For example, the existing Metabolic Theory of Ecology (MTE) explicitly addresses how metabolism (and therefore energy usage) scales across levels of organization from individuals to ecosystems (Brown et al. 2004). Because MTE considers constraints imposed by organism size, temperature, and stoichiometry on metabolic rates (Gillooly et al. 2001), it has the potential to leverage metabolism to explain global patterns (such as species diversity) across latitudinal or altitudinal gradients. However, despite these potential strengths, its applicability in practice has been limited (e.g., Bailly et al. 2014; O'Connor and Bernhardt 2018), debated (e.g., Hatton et al. 2019), and often justified using unrealistic assumptions and graphical presentations (e.g., log–log plots) that reduce the apparent magnitude of deviations from the theory that occur at large scales (Brown et al. 2004). Through the lens of our framework, we call for measures to include the four resources and interactions in ECSI which aim to provide a comprehensive understanding of potentially scale-independent processes that can explain deviations from MTE that are often ignored in assessments of that theory. Moreover, the ECSI system based approach complements and extends MTE down to molecular and cellular processes and includes other important

resources that are currently unaccounted for in the MTE.

Specifically, ECSI provides a framework for theoretical examination of the hierarchy of life that integrates energy and information, conductance and storage at *all scales*; thus helping us address life in a substantially broader way, both accounting for similarities across all living systems as well as the diversity that emerges from differences in how the ECSI resources are being stored and conducted by different living entities. Additionally, ECSI provides a path for extending the application breadth of formal tools that have been demonstrated to be successful working within individual ECSI resource types. For example, network analysis (Gosak et al. 2018) is a theoretical framework that has already been used to address the organization of life at a variety of scales from molecules (e.g., Li et al. 2019; Qin et al. 2020; but see Flint and Ideker 2019) to metacommunities (e.g., Economo and 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., Valentini et al. 2020 a; Nightingale et al. 2015; McGregor and Horn 2015; Franz and Nunn 2009). The ECSI framework suggests that these network-level descriptions of information can be augmented with conductance constraints (which restrict the ability for information to flow), and storage assets (which mitigate informational deficits) while also explicitly accounting for energetic input and use (which ultimately fuel these processes). Thus, ECSI provides a nexus on which quantitatively new theories can be built to illuminate novel integrative perspectives across living systems.

Application of the ECSI framework across scales

In Fig. 2, we provide basic examples of how ECSI can apply at all scales from ecosystem to molecular scales and we expand to a more detailed explanation in Table 1. To show the generality of this approach, we shift focus at the organismal scale from humans to plants in Fig. 3. Across these telescoping scales (Fig. 1C), (free) energy is ultimately provided by sunlight; however, more refined views of energetic flows and stores are depicted at lower scales that illustrate how resources move across scales and are instantiated in different forms. For example, energy from the sun at the ecosystem scale (Fig. 2A) is represented at cell and molecular scales as high-energy photons absorbed by photosystems in plant chloroplasts and used to split water into hydrogen and oxygen and move electrons to higher energy levels (Alberts et al. 2014; Fig. 3C and D). Just as energy appears at all scales (albeit in different forms), so does storage and

conductance. At the ecosystem and community scales (Fig. 2A and B), limitations on the availability and processing rate of energy from the sun are mitigated by stores of fixed carbon in populations of fish or artificial electrochemical cells, just as glucose at the cell (Fig. 2E) and molecular scale (Fig. 2F) reduce the dependence of small-scale processes on immediate access to high-energy photons or electrons (Alberts et al. 2014).

Moreover, a reduction in the uncertainty about availability of energy is achieved via collective efforts of human civilization such as through agriculture, where energy is stored from the primary production from plants; human land-use decisions reduce the information needed to meet energetic demands in an otherwise uncertain environment (Fig. 2A and B). Similarly, human blood sugar and long-term stocks of lipids reduce uncertainty about energetic availability (Fig. 2C and D) and allow the heart to beat continuously, and glucose stored within plant tissue allows for cellular respiration to continue in plants even at night (Alberts et al. 2014; Fig. 3C). Furthermore, environmental cues at different scales like daily variations that drive circadian clocks or the progression of seasons allow plants to take actions (e.g., by dropping leaves or timing reproduction) (Salmela et al. 2018; Fig. 3A and B) that reduce exposure to otherwise deleterious seasonal changes. At all scales, availability of energy (E) and other physical resources (e.g., water) are limited by conductance (C), and these limitations are mitigated either through managing storage (S) or making use of information (I) or a combination of both (Table 1).

Discussion: Unifying life-science research from genomes to phenomes to biomes

The ECSI framework described here aims to provide a broad and truly integrated view of life through the perspective of *resource limitations across biological scales*. Current approaches to mapping genotypes onto phenotypes recognize that the environment plays a critical role and that plasticity is highly quantitative (Schneider et al. 2020), but there is no general formulation for understanding how energetic and informational limitations constrain phenotypic expression and create selective pressures for conductance and storage adaptations. Incorporating energetics and information into phenotyping will facilitate multi-scale connections from genomes and their resulting phenomes to their ecosystems, potentially allowing for theories that connect global-scale phenomena like climate change to organism-scale phenomena like metabolic rate limitations as well as potential bidirectional feedbacks across these disparate scales. Life at all scales—from

bacteria to elephants and their ecosystem—is powered by metabolism and informational adaptations that manage the fundamental uncertainty related to finding and using energy and matter. Global warming not only accelerates metabolic rates by increasing the kinetic energy of biochemical systems (Yvon-Durocher et al. 2010), but it also increases uncertainty due to variability in weather patterns (Thornton et al. 2014).

Thus, formally incorporating limitations on the availability of energy and information into models of metabolic processes such as aerobic respiration and photosynthesis could lead to a comprehensive understanding of the complex interaction of genotype and environment that gives way to phenotype—allowing for a deeper understanding of how living entities respond to change across scales. There is no debate that living systems are sensitive to changes in both global-scale phenomena and micro-scale mechanisms of action, but differences in time and spatial scales have made general frameworks for connecting these two scales elusive. Our ECSI framework proposes to use energy, information, and the flow limitations and storage adaptations that relate to their availability as a connective tissue to build more inclusive models of life as a system of systems. Although we propose this framework to help scaffold new scientific theories for advancing life-sciences research, we also see the potential for framing broader discussion with the public about science that reduces the difficulty in communicating topics such as the difference between weather and climate (i.e., differences that are related to understanding scale).

Conclusion: Societal and pedagogical implications

The reintegration of biological investigation through the ECSI framework, as outlined here, will impact several dimensions of the scientific enterprise. While scientific progress continues to require in-depth scientific inquiry at each scale, there is increasing interest in understanding how processes at different scales interact and what aspects of systems depend upon or are invariant to changes in their scale (West 2018). Frameworks like ECSI can help facilitate information exchange across disciplines to better understand what phenomena in nature are scale dependent, scale agnostic, or emerge from interactions across scales and thus avoid the need to address whether scaling is complex or simple (Wimsatt 1972). As a way of doing science, 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. Finally, 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. We suggest that the ECSI approach will provide a framework that facilitates this integration, in part by offering a common vernacular that will be relevant across all scales of life.

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Data availability

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Appendix: Quantifying information

The process of uncertainty reduction has been quantified using a number of methods. Three common methods address fundamental components of the dynamic use of information. The first is Shannon's entropy, H (Shannon and Weaver 1949), defined here for a discrete random variable as:

$$H = - \sum_{i=1}^n p_i \log(p_i) \quad (1)$$

where n is the number of mutually exclusive outcomes of the random variable, and p_i is the probability of the occurrence of each outcome (i). Shannon entropy has been used as an index of the complexity or uncertainty of a system, for example in the diversity of signals in a communicative system (Freeberg and Lucas 2012) and the level of heterogeneity of a landscape (Vranken et al. 2015).

The second is Shannon's mutual information, $I(X; Y)$ (e.g., Bergstrom and Rosvall 2011):

$$I(X; Y) = H(X) - H(X|Y) \quad (2)$$

where $H(X)$ is Shannon's entropy relative to some random variable X , and conditional entropy $H(X|Y)$ is the entropy of the random variable X conditioned on the known value of the random variable Y . Thus, Shannon's mutual information is a measure of the reduction in uncertainty in state X based on the detection of some known value of state Y . Shannon's mutual information has been used to evaluate the

quality of the neural representation of sensory stimuli in the nervous system (Fairhall et al. 2012) and in understanding the role that habitat variation plays in species distributions (Donaldson-Matasci et al. 2010).

Shannon's entropy is a measure of the diversity in a distribution of possible outcomes, and mutual information is a measure of reduction in that diversity. It is also possible to quantify the effect of information on probabilities themselves. Bayes Theory (e.g., Dall et al. 2005) provides a method for evaluating an updated probability distribution $\Pr(A|B)$ describing some random physiological or environmental variable (A) given the presence of some signal or other source of information (B),

$$\Pr(A|B) = \frac{\Pr(B|A) \Pr(A)}{\Pr(B)}, \quad (3)$$

where $\Pr(A)$ is an initial (or prior) distribution of the variable before information is gathered, $\Pr(B|A)$ is the probability (or likelihood) that some information source B is consistent with a specific value of variable A , and $\Pr(B)$ is the probability of detecting the information source B under any level of variable A . Thus, Bayes Theorem provides an explicit measure of the frequency distribution of some relevant environmental variable conditional on the detection of some source of information. Bayes Theorem has been used to quantify optimal updating of estimates of the distribution of food resources by foraging animals (Dall et al. 2005), and to understand the decoding rules that result in organismal development (Petkova et al. 2019).