



NSF JUMPSTART

Understanding Drivers of Variation and Predicting Variability Across Levels of Biological Organization

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Based on a Jumpstart-Reintegrating Biology Vision Paper, developed during Town Hall meetings funded by The National Science Foundation in 2019-2020.

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Synopsis Differences within a biological system are ubiquitous, creating variation in nature. Variation underlies all evolutionary processes and allows persistence and resilience in changing environments; thus, uncovering the drivers of variation is critical. The growing recognition that variation is central to biology presents a timely opportunity for determining unifying principles that drive variation across biological levels of organization. Currently, most studies that consider variation are focused at a single biological level and not integrated into a broader perspective. Here we explain what variation is and how it can be measured. We then discuss the importance of variation in natural systems, and briefly describe the biological research that has focused on variation. We outline some of the barriers and solutions to studying variation and its drivers in biological systems. Finally, we detail the challenges and opportunities that may arise when studying the drivers of variation due to the multi-level nature of biological systems. Examining the drivers of variation will lead to a reintegration of biology. It will further forge interdisciplinary collaborations and open opportunities for training diverse quantitative biologists. We anticipate that these insights will inspire new questions and new analytic tools to study the fundamental questions of what drives variation in biological systems and how variation has shaped life.

Introduction

Variation is a fundamental property of biological systems, and while its significance has often been overlooked, the idea that it is important is not new (see Bateson 1894; Schmalhausen 1949; Waddington 1957; Hallgrímsson and Hall 2011). As a group of scientists from multiple disciplines, we define a biological system as a group of entities that interact and influence each other within the context of life (Table 1). Genes, proteins, cells, organisms, populations, species, communities, and ecosystems all exhibit and/or experience variation. Yet biologists often focus on studying the mean

(e.g., Williams 2008; Hey 2011). Although the mean, median, and mode are convenient summary statistics, they overlook biologically meaningful variation. In addition, variation in a biological process may be overlooked and dismissed as an artifact of imperfection in data collection (e.g., due to the precision of measurement instruments or human error). Thus, it is important to distinguish between variation that emerges from a biological process and variation that is due to observation error. All biological disciplines are grappling with the emerging realization that variation can have important implications. However, we lack a framework

Advance Access publication July 14, 2021

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Table 1 Definition of terms as used throughout the paper.

Term	Definition
Biological system	A group of entities—e.g., genes, proteins, cells, organisms, populations, species, communities, and ecosystems—that interact and influence each other within the context of life.
Level of organization	A class, layer, or grouping of biological organization, such as molecular, organismal, population, ecosystem, etc.
Variation	Deviation or divergence in the structure, character, or function of molecules, genes, cells, organisms, species, populations, or communities from those typical or usual in the group.
Scale	Spatial, temporal, or other measurable units.
Noise	Variation that is a result of measurement error or other artifacts that cannot be explained. This variation is often dismissed as “irrelevant.”
Driver	An underlying cause (e.g., modifier, mechanism, determinant) of variation or any other biological phenomenon.
Plasticity	The ability of a single genotype to produce different phenotypes in response to changes in environmental conditions.

that connects the causes and consequences of variation across different levels of biological organization and, to some extent, the tools to distinguish meaningful variation from measurement error in biological systems. As technological advances improve our ability to quantify variation in biological systems, we will be able to determine the mechanisms that drive variation, the impact of variation on the function of biological systems, and how future changes in variation may impact the biology of living systems on Earth.

It is axiomatic that the habitats of all living organisms are variable: they change over time and the surrounding abiotic conditions and co-inhabitants are diverse. Rainfall patterns shift; temperature fluctuates; earthquakes shake, causing the terrain to ascend or descend; and organisms evolve and go extinct. Phenotypic differences may be caused by intrinsic (genetic) variation or plasticity, leading to the ability of populations to respond to changing environments. Phenotypic plasticity allows organisms to respond individually to environmental changes in ways that may increase their probability of survival (e.g., [Strathmann et al. 1992](#); [Hadfield and Strathmann 1996](#)). Heritable variation provides the fodder for evolution ([Lewontin 1970](#)), in which selection may shape organisms into forms that will survive critical changes in their abiotic and biotic environments.

Identifying the drivers of variation and how variation interacts with the basic fundamental principles of biological systems will allow scientists to make predictive models that can be applied to systems or levels in which it might not be possible to make direct measurements. The ability to determine the drivers of variation at one biological level, and what influence it has, if any, on other levels, crosses disciplinary divides and unifies biological principles and theories. Here we explain what biological variation is and how it has been treated in the past. We discuss why studying variation and its drivers is important for understanding biological systems, outline potential barriers and solutions to studying biolog-

ical variation, and detail challenges and opportunities that may arise by studying drivers of variation across levels of organization in biology.

What is variation?

The Oxford English Dictionary defines variation in biology as, “Deviation or divergence in the structure, character, or function of an organism from those typical of or usual in the species or group.” We expand this definition to include molecules, genes, cells, species, populations, or communities, in addition to organisms ([Table 1](#)). Although in statistics the term “variance” refers to an index that quantifies the spread of a measure from a mean of a population, here we use “variation” to refer to the nature of the differences between entities in a biological system or changes in a system over time. In other words, we use the term “variation” interchangeably with difference, diversity, and disparity (e.g., [Hopkins and Gerber 2017](#)). Differences can be measured in a range of biological, physical, spatial, and temporal scales. However, variation is specific to the properties of a system (or its entities) and its environment. Some examples of variation include diversity of species, phenotypic differences in a population, or different alleles of a gene.

Variation can be stable or dynamic, depending on the processes that drive variation and the biological system in which variation is observed. Some variation may seem stable and in a steady-state. For example, the climatic conditions experienced by short-lived aquatic organisms may seem very stable and the allele frequencies of a population will not change over the lifetime of an individual within that population. In contrast, variation can be dynamic. For example, the daily weather patterns experienced by an individual can be variable (e.g., [Sears et al. 2011](#)) or the expression of alleles may change at a pace that is faster than the lifetime of an entity through mechanisms of plasticity, including epigenetics (e.g., [Carneiro and Lyko 2020](#)). Furthermore, variation detectable at one temporal scale may be invis-

ible at another. For example, in regard to seasonal cycles of variation, those measurements taken at one point may not be a true representation of the system (Fig. 1). The transition between dynamic and static variation depends on the temporal and spatial scale at which variation is measured and/or the nature and type of variation measured.

Variation could be beneficial for some systems and detrimental to others. Ecosystems such as tidal wetlands depend on daily changes in water levels, and some species rely on high levels of disturbance (variation in abiotic and biotic factors) for colonization (e.g., [Lake and Leishman 2004](#)). Other systems, such as many cellular processes in endotherms, rely on stable environmental conditions ([Levins 1968](#); [Heinrich 1977](#)). There may even be an optimal amount of variation for certain systems. For example, the mix of behavioral types in a honey bee colony can determine the efficiency of its collective foraging behavior ([Cook et al. 2020](#)). Models provide one way to examine the amount of variation a system can withstand or requires ([Mosqueiro et al. 2017](#)) as we discuss in more detail below.

Why is variation important?

Given the ubiquity and significance of variation in biology and biological processes, an understanding of the causes, or drivers, of variation is important. Identifying the drivers of variation is important because variation: (1) is a universal concept across biology; (2) is fundamental for evolution; (3) is important for acclimation to changing environments; and (4) may cascade across levels of biological organization.

Variation is a universal concept across biology

Variation is an inescapable part of biology. This means that whether one studies molecules, genes, cells, organisms, ecosystems, or any other level of biological organization, biologists have to examine variation in some way. Sometimes this variation is treated as “noise,” to mean measurement errors or other artifacts that disrupt our understanding of a biological process ([West-Eberhard 1989](#); [Tsimring 2014](#)). But variation can be an essential part of the biological process we are trying to understand. We find variation among genes and gene expression at the molecular and cellular levels (e.g., [Carroll 2008](#); [Mereu et al. 2020](#)). We observe variation in traits of individuals, from morphological traits ([Donihue et al. 2018](#)) to behaviors ([Sih et al. 2004](#)) and in the plasticity of these traits ([Stamps 2016](#)). Relationships in ecological systems are variable, for example, microbial symbionts impact most eukaryotic organisms, and vary within individuals and environments ([McFall-Ngai et al. 2013](#)). The species composition in a habitat

can lead to variation among communities across space and time (e.g., [Karlson et al. 2004](#); [Borrvall and Ebenman 2008](#); [Magurran et al. 2010](#)). Ecosystems are variable, for example due to changes in environmental conditions and perturbations that lead to variation in global water and energy balances ([Houghton et al. 2000](#)).

Variation is fundamental for evolution

Variation is fundamental for the process of evolution ([Stebbins 1950](#); [Lewontin 1974](#)). Natural selection acts on heritable variation (i.e., the proportion of phenotypic variation that is due to genetic variance). Selective pressures can lead to the differential reproduction of individuals with certain traits, yet variation in the population is often maintained, including cryptic variation ([Gibson and Dworkin 2004](#)). The persistence of variation may confer resilience against environmental changes, and may result from frequency-dependent selection, or may result when extreme phenotypes have a disproportionate impact on the system as a whole (e.g., [Leitão et al. 2016](#)). For example, keystone individuals in social systems can have a disproportionate influence on the collective behavior of a group, like highly informative individuals that become tutors for others ([Modlmeier et al. 2014](#)). Additionally, the geographic range of a population can expand when individuals with extreme phenotypes occur at the edge of the range, such as longer-legged, faster jumping cane toads driving their invasion front in Australia ([Phillips et al. 2006](#)). Furthermore, the processes that underlie variation can be stochastic, for example, genetic drift may lead to variation among populations but tends to decrease variation within populations ([Wright 1932](#)). Studying the drivers of variation may help elucidate principles of evolution and diversification and uncover how variation in a population is maintained. Evolutionary processes impact multiple levels of biological organization, therefore the study of variation must occur at multiple levels.

Variation is important for acclimation to variable environments

The phenotypic outcomes produced by developmental processes are seldom fully pre-determined ([Waddington 1957](#)). Many organisms exhibit phenotypic plasticity, which is traditionally defined as the ability of a single genotype to produce different phenotypes in response to changes in environmental conditions ([West-Eberhard 1989](#)). For example, differences in temperature or photoperiod may lead to changes in animal coloration (Fig. 1, e.g., [Heldmaier et al. 1982](#)) or plant height ([Poorter and Nagel 2000](#)), also referred to as phenotypic flexibility ([Piersma and van Gils 2011](#)). Phenotypic plasticity increases the amount

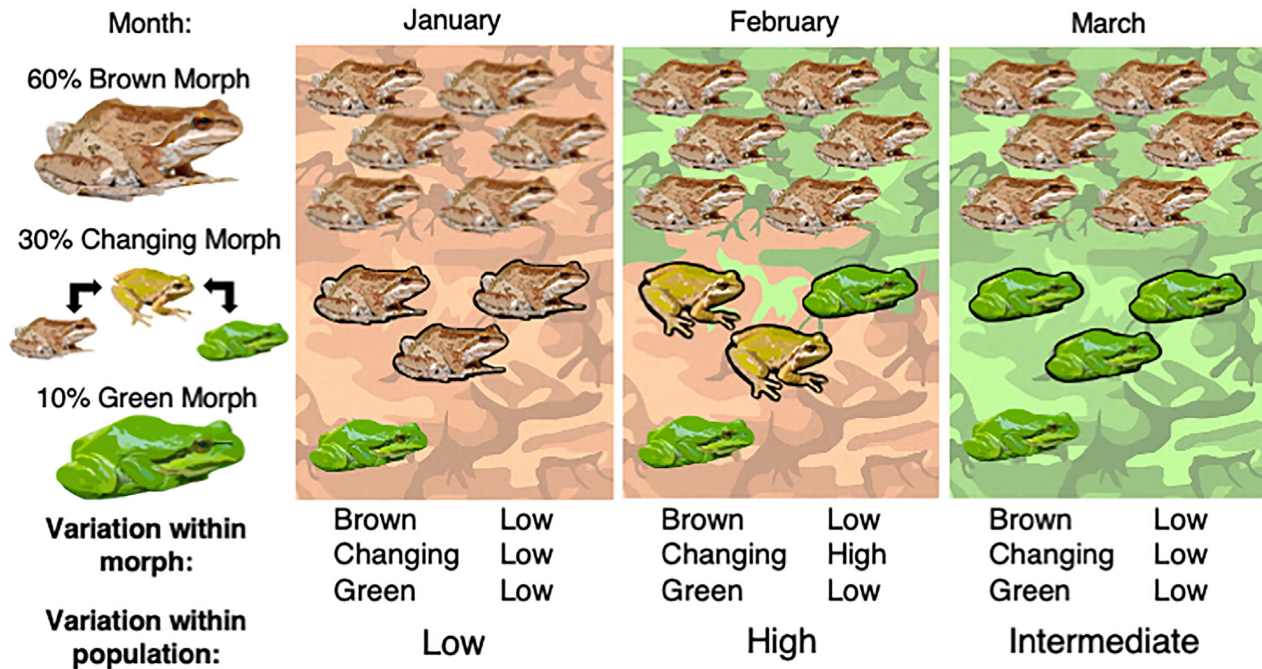


Fig. 1 Populations of the Pacific tree frog (*Hyla (Pseudacris) regilla*) exhibit three morphs: a brown morph, a green morph, and a color-changing morph. As the background vegetation turns from predominantly brown in winter to predominantly green in spring, the population shifts toward a greater proportion of frogs with a green color, because of the dynamic coloration of the color-changing morph (darker outline in the center panels) (Wente and Philips 2003, 2005). Measuring color variation within each morph, or within the larger population, in different months would lead to different conclusions regarding color variation. Original illustrations and graphic design by Mitch Beito.

of phenotypic variation that can be produced with a single developmental “toolkit” allowing organisms to rapidly respond to changes in environmental conditions. When the geographic range of a species or a population spans diverse environments, individuals may experience different selective pressures. For example, phenotypic variation across species’ ranges can result from genetic variation or plasticity in dispersal among benthic marine animals (Hadfield and Strathmann 1996). In general, differences in selective regimes can produce phenotypic changes, and so, variation in the environment can be viewed as a driver of variation in phenotypes (Grant and Grant 2014).

Variation may cascade across levels of biological organization

Variation at one level of biological organization may result in variation at another level (Fig. 2). For example, genetic variation at the cellular level may result in phenotypic variation at the organismal level, leading to bottom-up effects. Bottom-up drivers of variation lead to differences in a population because they have uneven impacts on individuals, for example, circulating hormones trigger stress responses or breeding unevenly in a population (e.g., Vitousek et al. 2019). Top-down

effects can include variation in the environment (Stein et al. 2014), such as changes in temperature, which can impact phenological differences across a species’ range (e.g., Morin et al. 2009; Kingsolver and Buckley 2018). Both bottom-up and top-down drivers likely interact to shape the biological variation observed. The interaction of variation across organizational levels is known as “bio-resonance” (Buiatti and Longo 2013), which may provide a unifying conceptual and mathematical framework for understanding constraints and amplifications of variation among organizational levels.

Key barriers to studying variation across biology

The complexities of biological systems, especially when observed across multiple levels of organization, can limit our ability to determine the causes and consequences of variation. We identify five key challenges to the study of variation: (1) difficulties in measuring variation; (2) determining what is a driver; (3) drivers of variation are not the same within or across biological levels; (4) examining variation at one level may overlook variation at a different level; and (5) causes and consequences of variation are intertwined across levels.

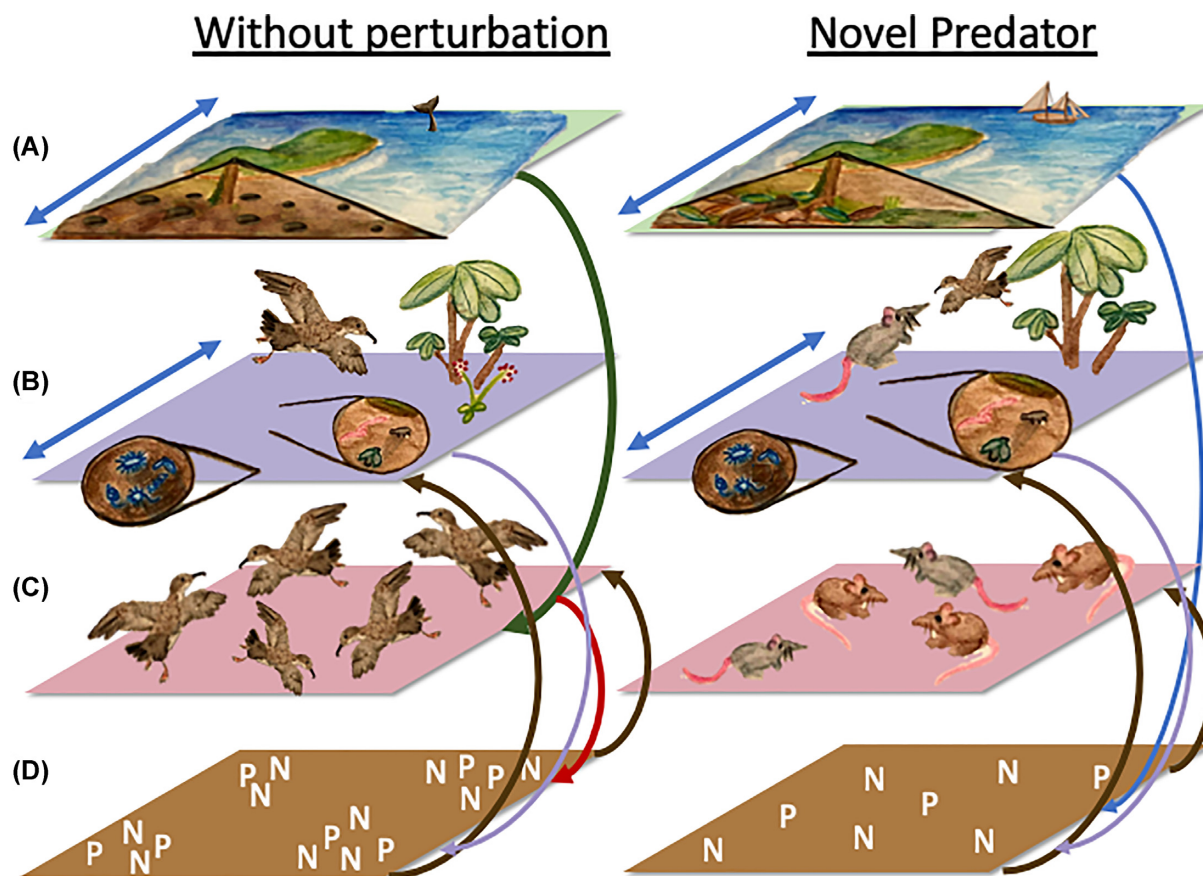


Fig. 2 Variation at one level can be impacted by variation at other levels. This figure is based on a study of the impact of rats as an invasive predator on an island in New Zealand (Fukumi et al. 2006). The study focused on how changes in one species can impact processes at other levels of organization. Arrows represent the impact that variation at one level may have on another. The weight and direction of the arrows suggest the strength of the impact for this specific example. (A) represents the ecosystem level at two size scales, from micro- to macro-scope, as indicated by the blue arrow on the left side. (B) represents the community level at multiple size scales, from micro- to macro-scope, as indicated by the blue arrow on the left side. (C) represents the population level, focusing on one species in each circumstance. (D) represents the molecular level of nitrogen and phosphorus abundance and change in spatial distribution.

Difficulties in measuring variation

Variation is the quantitative or qualitative difference(s) between two or more samples. The biological level of organization, spatial and temporal scales, and measurement methods of such variation may differ widely across disciplines. There is no universal approach to measuring variation across biological systems. The lack of a general approach has led to the development of system-dependent methods and technologies for quantifying variation. Despite technological advances, measuring variation at extremely large or small spatial and temporal scales can be expensive or inaccessible. Furthermore, it is important to distinguish between meaningful biological variation and variation that results from measurement error, insufficient data, or abstractions when converting the real world into quantitative measurements (Regan et al. 2002). The diversity of experimental protocols used to collect samples and the computational pipelines used to process and an-

alyze variation comprise a disparate collection of resources. However, we may find similar statistical analysis tools and data processing pipelines that could be integrated into a common and general framework. It is also noteworthy that the ability to measure variation at very fine or very broad temporal or spatial scales, or across biological levels, may not be appropriate or helpful in pursuit of all questions. Determining the appropriate scale of measurement is a challenge to studying variation.

Determining what is a driver

A statistical association between measured values at one biological level is not sufficient to identify the measured variation at that level as a driver of variation in another. Correlation does not imply causation and carefully designed studies are required to resolve the direction of a relationship and to determine what is a driver and what factors co-vary with variation. For example, in a group

of individuals, behavioral variation might be correlated with genetic variation, however, it might not be known if the genetic variation is indeed the cause of the observed behavioral variation or, for example, it is influenced by ecological processes (Page et al. 2018).

Certain types of variation might be explained by more than one driver. Finding out how many drivers underlie a particular type of variation and their relative importance could be a challenge that opens up opportunities for discovery. For example, most phenotypes are determined by multiple genes that contribute unequally to the expression of a phenotype, and identifying genes with large effects is a major goal of many studies of quantitative genetics (e.g., Hayes and Goodard 2001). Drivers may further interact with one another, and disentangling their effect could be a challenge worthy of investigation. To give a brief example, seasonal forms in the color patterns of some butterfly species result from a complex series of developmental and environmental causes, none of which can reasonably be said to be the “fundamental” driver of the phenotypes in question (Roundtree and Nijhout 1995; Hartfelder and Emlen 2012). In the buckeye butterfly *Junonia coenia*, the hormone ecdysone plays an important role in color pattern determination (see Fig. 7, Hartfelder and Emlen 2012). However, ecdysone secretion is itself regulated by another endocrine factor known as prothoracicotropic hormone (PTTH), and the secretion of PTTH is partly determined by temperature and photoperiod, making the entire signaling cascade environmentally sensitive. In cases such as this, there are a number of distinct developmental drivers of the phenotype, rather than a single causal mechanism that acts in isolation.

Drivers of variation are not the same within or across biological levels

Variation at one level of biological organization may dampen, amplify, or be independent of variation at another level. A driver of variation at one biological level may decrease variation at another level. For example, drift can cause variation among populations but eliminate variation within a population (Wright 1932). Similarly, different genetic variants may result in the same phenotype or in multiple phenotypes because of differences in gene expression. Furthermore, the way in which a driver at one biological level influences variation at another one is not always consistent—sometimes a certain driver will lead to variation, and at other times it will not (Roth 1991). For example, mutations in a gene at the molecular level often lead to variation in a phenotype at the organismal level. However, a mutation in a non-coding region of the genome will produce vari-

ation among genomes, but these differences generally will not result in variation among organisms in an observable trait. Similarly, behavioral variation among individual ant workers sometimes, but not always leads to variation at the population, or colony levels (Pinter-Wollman 2012; Jandt et al. 2014; Horna-Lowel et al. 2021). Whether variation is adaptive, maladaptive, or neutral (Scheiner and Holt 2012), may control what drives variation and how it impacts features across levels of biological organization.

A driver of variation may influence phenomena at multiple levels of biological organization or in many systems within a certain level. For example, differences among alleles of a gene drive variation in the phenotypic traits that they code for, which can lead to variation among groups of organisms, different populations, or across entire ecosystems. Similarly, the environment can drive variation among individuals or populations via plastic developmental responses or differences in adulthood, such as the variation observed in circulating hormonal titres (Husak et al. 2021). Variation can have limits due to physiology, for example, for organisms with determinate growth, a maximum body size implies that there is a threshold to variation (McMahon 1973). Identifying the drivers that limit organismal size can potentially identify the drivers of size variation. Comparisons to species with indeterminate growth (as found in some reptiles, amphibians, and fish) may help uncover when drivers of variation are relaxed or constrained. Variation in animal body size may in turn predict variation in locomotor speed both within a population and across evolutionary lineages (e.g., Bauwens et al. 1995). How many levels of biological organization one chooses to, or is able to, study will influence the way in which drivers of variation are uncovered. For example, identifying a mutation in a genome that leads to variation in a certain morphological trait might provide a sufficient explanation for variation observed in the morphological trait. However, we might want to probe further and deeper into the molecules that form the genes, patterns of polarity, cell–cell interactions, tissue-specific responses to signaling molecules, or competition between anatomical characters to dissect the drivers of variation further.

Examining variation at one level may overlook variation at a different level

Measuring variation at one level may not lead to detecting important variation at a different level. For example, a study of cancer may measure variation among cells, but it might not detect variation among organisms in response to the measured variation at the cellular level (Soto et al. 2016a, 2016b). Similarly, a study

of variation in how different species fit wetland restoration efforts may overlook genetic variation among soil microbes and their ability to filter water, which may be crucial to the success of the restoration effort. A long-overlooked source of variation is the microbiome. As we increase our ability to quantify and understand organisms as holobionts, linking variation in the microbial environment of an organism to variation among organisms is expanding our understanding of the drivers of variation at multiple levels of biological organization (Dittami et al. 2021).

A challenge in detecting variation at one biological level, when studying another, stems from the different temporal scales over which changes occur and the spatial scale at which variation can be detected at different biological levels. For example, if a snapshot of a population is taken at one point in time or one location, then the amount of variation measured may not be the same as the amount of variation detected when examining longer periods or larger spaces (Fig. 1). Such a mismatch in time-scales can also occur when studying ecological communities with species that have different generation times, or when endogenous periodicity is different from external environmental periods. Certain systems experience seasonal, daily, or hourly fluctuations in measured parameters, and the period of this fluctuation should be accounted for when examining variation in the system. Thus, the study of variation requires defining the temporal and spatial scales at which differences are being examined and the biological system within which variation occurs.

Causes and consequences of variation are intertwined across levels

Variation at one biological level can have consequences that reverberate to other organizational levels. This influence is a challenge to the study of variation because a focal phenomenon cannot be addressed by examining a single driver at a single biological level of organization, without considering the consequences of variation at other levels. The consequences of variation may influence which drivers we search for and where (i.e., at which temporal and spatial scale) we search for them. The concept of “nested ecosystems,” developed by McFall-Ngai et al. (2013) stresses the impacts that changes at one level of organization, e.g., rats in an ecosystem, have on, e.g., the presence of nesting birds, the feces the birds may deposit, thus the fertilizer present for plants and the resulting plant communities and ultimately the microbiomes in the guts of all animals present (Fukumi et al. 2006, Fig. 2). Thus, variation

at one biological level might influence processes at other levels or in other biological systems within the same level of organization. Such influence of variation across levels of biological organization challenges the tendency to rely on simplified scientific explanations that aim to explain a single phenomenon by pointing to a single causal factor at a single level of biological organization.

The study of variation requires identifying the organizational level of both the variation that is being studied as well as the levels at which the causes and the consequences of the variation occur (Fig. 2). The relationships among processes across levels of organization are often non-linear, adding complexity to the study of such links. Being able to make predictions about the causes and consequences of variation at one level of organization and the concomitant effects on other levels may offer a broad understanding of phenomena that are difficult to directly measure. For example, by modeling the activity time and behavior of individual digisalamanders of multiple size/age groups based on physiological models and a behavioral rule, one could predict activity patterns and potentially population structure of a species in a specific area (McEntire and Maerz 2019). Actual activity time and population structure for salamanders are difficult to directly measure because they are cryptic species and spend much of their time underground. The fact that biological levels are interlinked can be viewed as an opportunity because it allows us to step outside of our narrowly defined areas of professional specialization, and collaborate with colleagues in other areas of biology that we might not currently interact with on a regular basis. The potential for causal feedback between variation at different levels of organization allows for an integration of research programs that focus on a multi-scale perspective of biology.

Suggestions for overcoming barriers

The multi-level nature of biology and the potential cascading effects of variation at one level onto processes at a different one requires that the search for drivers of variation account for these complexities. Efforts to identify patterns of variation across levels of biological organization cannot be improved by simply collecting additional empirical data. A better understanding of the drivers and the consequences of variation can be obtained by (a) accounting for feedback between drivers and consequences; (b) designing a general framework for the study of variation; (c) using perturbations to identify mechanisms; (d) using modeling approaches; and (e) adapting existing tools and techniques from one field of biology to another.

Accounting for feedback between drivers and consequences

Because variation cascades across biological levels of organization, one solution to integrating investigations across biological levels is to study the drivers of variation in the context of their consequences, or outcomes. These consequences can help guide researchers to discovering the drivers that underlie the observed variation. Drivers and their consequences often occur at different levels of biological organization and therefore the integration of them can help resolve some of the challenges detailed above. For example, if a goal is to study the drivers of phenotypic variation in a population, considering the evolutionary consequences can illuminate the heritable drivers that underlie variation at the organismal level by considering outcomes of variation at the population level. In addition, the study of environmental (physical and/or social) features that drive variation may be informed by the study of the consequences that such variation has on how populations of different species interact. Thus, the study of drivers of variation stemming from processes at the ecosystem level can be informed by the study of the consequences of such variation at the community level (Fig. 2). Similarly, Read et al. (2018) found that community diversity of rodents was not only driven by temperature, but also by individual variation of body size in rodents. The authors associated these differences in variation of body size with narrower thermal niches, demonstrating the need to study drivers of variation at multiple levels of biological organization.

There may be feedback between the drivers and consequences of variation that could help guide how variation is studied (Fig. 2). Drivers at one level of organization might be influenced by forces and consequences at a different level. For example, top-down drivers of variation in a morphological trait, such as environmental pressures, can shape, and differentially select among traits that are shaped by bottom-up proximate mechanisms. Furthermore, genetic variation changes as a function of selection on the traits for which the genes code. This feedback across levels of biological organization can help create an integrative, multi-level approach to the study of the drivers of variation.

Designing a general framework for the study of variation

Because variation may take different forms at different levels of biological organization, there are multiple analysis pipelines and statistical tools for examining variation across levels of biological organization. Breaking down the types of variation and the components

of analysis pipelines may bring us closer to a uniform framework for analyzing variation. Variation can be classified in terms of its data type to indicate what set of statistical tools and data-processing pipelines might be useful for its analysis. Variation can be classified as numerical or categorical. Numerical variation can be continuous (e.g., differences in molecular weight) or discrete (e.g., number of mutations). Categorical variation may include any measure that takes one of a limited number of values (e.g., different atom types, residue mutations, types of disturbance, and color morph (Fig. 1)). Variation that depends on multiple drivers could be better modeled as a multivariate function. Depending on the data type and complexity, different statistical approaches will be suitable for quantifying variation. The accuracy of any statistical pipeline primarily depends on the quality of the sampled data, the biological system, and the temporal and spatial scales at which variation is measured. Whether or not we can identify a universal method for sampling and analyzing variation may determine our ability to reach general conclusions that integrate the study of variation across levels of biological organization.

One potential unifying framework could be Information Theory (Pierce 1980). Measures from information theory, such as information content or entropy could be used to quantify variation across and within levels of biological organization. Specifically, entropy accounts for the structure of the distribution of a trait rather than considering only the second moment of the distribution, i.e., variance. Furthermore, mutual information, another measure from information theory, can be used to quantify the dependencies between drivers and variation, both within and across levels of biological organization. This approach was originally developed to study telecommunications but has been adapted by many other fields such as computer science and biology. For example, in living organisms, information is propagated through many levels, from molecules (gene expression, protein–protein interactions) to social behaviour (Danchin et al. 2011). Information theory has been used to uncover how cells translate highly variable molecular signals into meaningful biological information that results in an accurate biological response (Selimkhanov et al. 2014), and has the potential to advance how we study variation in communication networks (Pilkiewicz et al. 2020).

Use perturbation to identify mechanism

Often, variation is detected, but the cause of it is uncertain. A common approach to determining the sources of variation is to manipulate the suspected driver. For example, one could change light exposure for a plant (Poorter and Nagel 2000) or species composition in a

community (Tilman et al. 2001). If the predicted variation does not emerge, we can try another suspected factor and perturb its occurrence, abundance, or character. This process is clearly iterative. For large perturbations, one can take advantage of a natural disturbance at a single site or a series of sites that differ in time since disturbance (i.e., a chronosequence; Pickett 1989). Such an approach has revealed that species diversity is greatest at intermediate levels of disturbance (Roxburgh et al. 2004) and intermediate positions along spatial gradients (the mid-domain effect; Colwell et al. 2004), but the magnitude of disturbance or domain limits depends on the specific system.

Using modeling approaches

Computer simulations and mathematical models can be useful tools for integrating our understanding of how different drivers influence variation at multiple levels of biological organization. For example, individual-based or agent-based models (ABM; Murphy et al. 2020) may be used to explore interacting drivers, and are, for example, being used with increasing frequency in ecological studies (Lomnicki 1999; DeAngelis and Grimm 2014; Grimm et al. 2017). Agent based models allow including different drivers of a pattern (Grimm and Railsback 2011) and testing the sensitivity of the system to each driver. Ecological forecasting is another tool for quantifying and predicting variability that is observed across scales (Dietze 2017). Ecological forecasting simulates spatial and temporal variability as well as unexplained variation due to model uncertainty, heterogeneity, and stochasticity, making it a potentially powerful tool for understanding variability across scales. However, it is important to remember that patterns found with computer simulations do not necessarily reflect actual empirical processes. Therefore, computer simulations can be helpful in rejecting certain explanations and producing predictions that then need to be tested empirically.

Adapting existing tools and techniques

The big-data era has revolutionized biology, from personalized medicine and genetic engineering (Hulsen et al. 2019; Navarro et al. 2019) to real-time remotely sensed observations of animal behaviors (Smith and Pinter-Wollman 2020) and ecological processes (D'Odorico et al. 2020). The increased availability of data allows unprecedented opportunities to measure variation across levels of biological organization. Artificial intelligence, machine learning, image recognition, and other technological advances make it easier than ever to process large amounts of data, but their potential for measuring variation has not been fully realized

because may still require many hours of manual labor (e.g., Younis et al. 2018). Applying advanced technological and analysis tools to the study of variation across levels of biological organization will require genuine collaborations between biologists, statisticians, computer scientists, and data scientists.

Several biological fields have successfully decomposed variation across temporal and spatial scales by adapting tools and techniques from other disciplines. Climate science uses wavelet analyses from physics to decompose climatic variation across temporal scales (i.e., seasonality, trends, and noise; Lau and Weng 1995; Vasseur and Yodzis 2004). Community ecology uses variance partitioning from statistics to distinguish sources of trait variation between individuals, species and sites (e.g., Ackerly and Cornwell 2007; Violle et al. 2012). At the organismal level, amphibian ecologists have used tools from biophysics (e.g., the physiology of water loss) to estimate differences in individual fitness across a species' range to predict habitat suitability in response to climate change (Gifford and Kozak 2012; Riddell and Sears 2015; Peterman and Gade 2017; Riddell et al. 2017, 2018; McEntire and Maerz 2019). The advances made possible by embracing tools from other disciplines and across spatial and temporal scales suggest that there is much to gain by a global synthesis of variation.

It may further be possible to adapt technologies that work at one level of organization to other levels. For example, remote sensing can be used to gather information on leaf reflectance and can also be used to study the evolution and diversification of plants (Meireles et al. 2020). Similarly, advances in cellular engineering have allowed *in vivo* incorporation of small molecule fluorescent reporters into specific proteins to study cellular trafficking patterns, an approach that has been limited to *in vitro* experiments previously (e.g., Wang et al. 2018).

Opportunities for reintegrating biology

Scientific education tends to be broad initially, but over time, professional pressures encourage researchers to become specialized, and focus on a particular organism or biological level. This specialization has resulted in the compartmentalization of knowledge that may hinder scientific progress. Many biologists agree there is a need to reintegrate fields, but it remains unclear how this should be accomplished (Wake 2003, 2008).

Evidence suggests that designing environments to support creativity, collaboration, and diversity promotes innovation, which should be a priority for funding agencies and institutional leaders. Indeed, some

of biology's greatest achievements have been a result of unique collaborations across disciplines. The Human Genome Project leveraged international collaboration and (almost instantaneous) data sharing to read and record the entire sequence of the human genome (Collins et al. 2003). The Intergovernmental Panel on Climate Change similarly depends on international collaboration and dissemination of scientific information for assessing climate change (Beck and Mahoney 2018). The Santa Fe Institute was created to understand the complexity of both natural and social systems at a time of growing concern for the hyperspecialization of science (Dillon 2001). Other synthesis centers, including NSF-funded Centers (NCEAS, NiM-BIOS, NESCENT, and a forthcoming Center for Open Environmental Data) as well as other synthesis centers around the world (e.g., sDIV/iDIV, CIEE, etc.) are evidence of the demand for and productivity of interdisciplinary collaborations. While bringing researchers together in physical spaces, and providing funding for collaborations are essential for integrating scientific disciplines, training students on how to work collaboratively is necessary too. Yet, biology training programs rarely train students on how to work collaboratively, initiate and maintain conversations that bridge disciplines, and integrate the science, data management and sharing, which are at the foundation of successful collaborations.

Historically, the university environment did not facilitate cross-disciplinary collaboration (Leshner 2004). To address this structural barrier, small, specialized departments are being integrated into large multi-disciplinary "life sciences" divisions and collaborative centers have emerged, becoming leaders in interdisciplinary research (e.g., Hackett et al. 2008). The organizational and physical structures (i.e., open coworking spaces) of these new institutions can create opportunities for chance interactions among researchers from diverse backgrounds. Spontaneous interactions facilitate innovation (Hoegl and Proserpio 2004), and the restructuring of university divisions should borrow recommendations from team science (Stokols et al. 2008). For example, small and diverse research teams innovate at a higher rate compared to large and homogeneous teams (Wu et al. 2019; Hofstra et al. 2020). Groups in large multi-disciplinary departments have ample opportunities to form such small and diverse innovative groups. Thus, as specialized departments become integrated into larger ones, the creation of smaller collaboration pods, or multi-PI teams, could facilitate innovation. However, collaborative efforts are not always diverse, equitable, or inclusive, despite the increased innovation that comes from diverse teams (Hong and Page 2004; Hofstra et al. 2020) and the increased difficul-

ties that traditionally excluded groups face (Chaudhary and Berhe 2020; Phillips et al. 2014; Halsey et al. 2020; O'Brian et al. 2020). Underrepresented minorities and scholars from the Global South are often excluded from, and less likely to seek out, collaborations (Rubin and O'Connor 2018; Stocks et al. 2008). The additional challenges of leading and participating in interdisciplinary research as a minority must be addressed by institutions and funding agencies (Hofstra et al. 2020). Required implicit bias (and bystander) training for all participants, leadership training, and building communities of practice are important steps towards cultural change. A core principle of reintegrating biology should thus value diversity, equity, and inclusion as primary drivers of innovation.

Conclusions

Our ability to reintegrate biology hinges on uncovering the causes and consequences of observed variation at different levels of biological organization. The study of the drivers and consequences of variation will advance our general understanding of biology by developing multi-level approaches that integrate across systems, levels of biological organization, and temporal and spatial scales. Understanding the drivers of variation at one level of organization, and the consequences variation has on other levels, will help set priorities regarding the type of data collected and the ways in which it is analysed. An integration across biological levels and study systems requires not only breadth of thought and expertise but also new tools and analytical approaches that still need to be developed. The importance of uncovering the drivers of variation is clear when considering the changing world in which we live.

Acknowledgments

We would like to thank the organizers of the 4 NSF Reintegrating Biology Jumpstart meetings as well as the facilitators at the meetings in Austin and San Diego specifically. These meetings allowed for the production of this manuscript. We would also like to thank Suzanne Miller for organizing this special issue and the associate editors and reviewers who give invaluable feedback.

Data availability

No new data were generated or analyzed in support of this research.

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