

Rescaling biology: A call for integration across disciplinary scales for enhanced understanding and prediction

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Question, Exciting Science, and Potential Impacts:

Given that we see interactions at distinct scales, as we cross scales, how do we develop an integrated framework?

The organization of the living world covers a vast range of scales, from molecules to the biosphere. As biologists working within disciplines, we tend to focus our research on a limited range of scales, therefore developing sufficient understanding of complex processes across biological disciplines requires frameworks that allow us to test questions and make predictions across scales. For instance, does genomic variation within populations allow us to explain community structure? Do the dynamics of cellular metabolism translate to our understanding of whole ecosystem metabolism? Frameworks that enable scaling across levels would ideally allow us to test hypotheses about the degree to which explicit integration across biological scales is necessary for predicting the outcome of biological processes, from both the higher and lower order levels. Do processes scale seamlessly across biological organization or are there fundamental transitions that limit our ability to make predictions at higher levels? Similarly, can sub-organismal processes be sufficiently understood in isolation of potential feedback from the population, community, or ecosystem levels? And can we infer the sub-organismal processes from data on the population, community, or ecosystem level? Concerted efforts to develop cross-disciplinary frameworks will open doors to a more fully integrated field of biology.

Scaling predictions in integrated biological systems is particularly pressing in the face of our rapidly changing world. Human induced stressors such as our impact on climate, the introduction of environmental toxicants, land-use change, the spread of invasive species, and the increase and persistence of pharmaceuticals in both natural and anthropogenic settings, are affecting biological systems on a wide scale, from microbes to vertebrates. More importantly, these stressors have effects at multiple fundamental levels, from molecular interactions to community-level host pathogen dynamics to the ecosystem of the planet as a whole. Climate change may threaten a biome through its effect on ecosystem-level processes. These ecosystem dynamics may themselves be driven by effects on community structure, which in turn may be explained by effects on the fitness of populations of individual species, and of course the fitness of members of any species will be affected by processes acting at an even smaller scale. The fate of populations may come down to effects on how individuals maintain homeostasis or allocate resources, which are the result of physiological systems built on processes at successively smaller and smaller levels of biological scale. How can we make predictions about the effects of climate change that incorporate the links and feedbacks that may exist across these scales? These same issues pose barriers to comprehensive approaches

to a myriad of other critical challenges. For instance, the effects of an emergent pathogen start at the level of molecular interactions but ripple out to whole organisms, host-pathogen dynamics, and ultimately the community structure and services of an entire ecosystem. Studying each of these levels in isolation may lead to erroneous predictions in overall outcomes at different levels if these processes are inherently integrated across scales.

Identifying, developing, and refining frameworks that work to integrate biological data across scales will allow biologists to begin connecting research at their given level(s) of biological organization to produce more nuanced and complete pictures of biological systems. Significant barriers to such frameworks include identifying the scales and boundaries of biological processes, identifying commonalities across scales, developing testable hypotheses about integration across scales, and identifying and developing empirical systems in which these hypotheses can be rigorously tested. We urge the biological community as a whole to work towards overcoming these barriers, which we outline below along with some potential avenues for moving forward towards a reintegrated discipline.

Why Now:

There is ample research and conceptual development at a wide array of scales and an urgent need to make accurate predictions about how the biotic world will respond to multiple axes of anthropogenic change. We are at a tipping point due to a confluence of rapid data production, computational tools, novel instrumentation, and multi-scale problems that demands that we develop these frameworks to address key biological problems. The new framework(s) and lines of research we advocate will enable us to more effectively address climate change-related challenges and human health and welfare by developing predictive capacity. We will gain insight into complex systems such as the interactions between hosts and their microbiome and the dynamics of infectious disease from pathogen infection to community consequences.

Elaborate on key barriers/challenges that need to be overcome:

1) Find the scales and boundaries of biological structures and processes.

Traditionally, scales in biology are described as atomic/molecular, subcellular, cellular, organismal, population, community, ecosystem. However, these traditional scales may miss the levels of complexity within different units at a particular scale (e.g., a bacteria with different metabolic capabilities). Within the discussion of scales, the complexity and heterogeneity implicit within traditional scales will need to be investigated and described to improve our understanding of biological scales and units. Heterogeneity generally decreases with increasing scale (Levin 1992), and heterogeneity may increase the variation in biological processes (Levin 1992, Collins et al. 2018).

Different units across scales can perhaps be thought of as Russian nesting dolls, with some situations in which all dolls are nested and dependent on each other, some in which none of the dolls are nested (do not depend on each other), and an intermediate case. Developing the framework(s) to assess the effect of scale and integration will probe the extent to which biological systems are parallel, hierarchical, or hybrid.

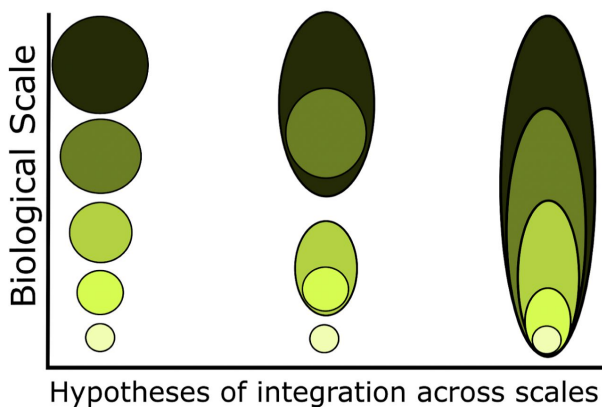
Biological processes and scale. Although structural scaling is primarily resolved with mathematical tools (e.g., mass balance models), a more fundamental theoretical and empirical challenge is that relevant processes generating biological patterns often depend on multiple interacting scales. Therefore, scale boundaries and transitions are uncertain (Wiens 1989, Scholes 2017) but essential to begin to resolve. A first step towards understanding the scale of biological processes is to identify at which scale boundaries certain biological patterns are changed versus maintained across biological systems (Scholes 2017).

Cross-scale interactions of pattern and process. A second challenge is understanding where broader-scale factors influence local controls on biological processes (e.g., Rose et al. 2017, Scholes 2017). Thus, a second step is to identify cross-scale interactions that may explain different scaling relationships. Biological interactions generate emergent patterns and behavior that may not be predicted based on observations at single or multiple, independent scales (Peters et al. 2007). For example, biological relationships may be independent across scales (parallel), dependent on some scales but not others (intermediate), or be nested hierarchically (hierarchical) (Figure 1).

2) Identify analogous units (structure) and processes (functions or interactions) across scale to enable “translation” across scales.

Biology is currently largely disintegrated in fields that correspond to different levels of organization, i.e., scales. Thus, in building any unifying or general framework across disparate scales we are necessarily also facilitating communication across the fields within biology. Translation of common phenomena must be a first step in both communication across fields and in attempting to apply existing frameworks from one scale at another and in developing new common frameworks. We would argue that a means to that translation is to recognize and characterize basic “units” as well as fundamental forms of interaction that comprise the dynamics at a single scale.

Figure 1. Conceptual illustration of patterns of biological scaling that differ in relative hierarchical dependence.



We certainly already recognize units at many scales and categorize them as of the same type or different type. For example, we have molecules of the same and different type, likewise cells. We characterize whole organisms (i.e., individuals) of the same and different species, groups of organisms as populations, communities of different organisms, and habitats or ecosystems of different constituents. We advocate that as biologists attempt to make

predictions across scales we will all need to consider which units are analogous in a framework that is based on interactions among units.

Table 1. Examples of similar terms used across biological scales.

General Term	Definition	Scale	Specific Term
+/0 interaction	positive for one participant but neutral for another	cellular/molecular	extracellular metabolites
		population/community	commensalism
-/0 interactions	negative for one participant but neutral for another	cellular/molecular	inhibitor
		population/community	interference
+/- interaction	positive for one participant but negative for another	cellular/molecular	inhibitor
		population	exploitation
		community	predation
++ interactions	positive for both	cellular/molecular	activator, promotor
		population	cooperation
		community	mutualism
-/- interactions	negative for both	cellular/molecular	mutation
		population/community	competition
rate	the pace of a transition or process over time	molecular	kinematics
		cellular	metabolism
		population	growth
		community	trophic dynamics
		ecosystem	flux

Similarly, forms of interaction among units, and phenomena that result, may also have analogues across scales. The most general framework will necessarily have to think of these interactions in the most general terms and those general terms will require translation or specification in the language of research at each particular scale. Perhaps this might look

something like what is presented in Table 1. In other words, we will need to agree upon a common and general language that captures key processes and identify field-specific terms that are at least sufficiently synonymous to enable general framing.

3) *Develop framework(s) that unite multiple scales, including alternative hypotheses of scaling up.*

As we look to describe the interactions that occur across all biological scales, it becomes essential to develop a set of frameworks that allow behaviors to be predicted across scales, even in the absence of data at one particular scale. Utilizing existing and generating new framework(s) will allow researchers to (i) develop testable hypotheses regarding interaction and communication between units (ii) drive the development of novel tools and instrumentation to allow probing of systems at various scales, (iii) identify if the processes build across scales (e.g., are additive) or are nested, and (iv) allow further refinement or modification of the frameworks to better model biological systems. In addition, the framework(s) will allow researchers to determine the extent to which various scales (and bounds) are nested vs. parallel (Figure 1), potentially identifying “break points” at which one framework no longer accurately predicts both larger and smaller phenomena, and allowing for the development of alternative hypotheses of scalability.

It behooves us to identify current frameworks used by fields both within and outside of biology. Some more general theories, such as systems and network theory (Bronfenbrenner 1992, Caldarelli 2007) may reach across scales readily, whereas other more field-specific frameworks (e.g., adaptive radiation, ecological succession, Chemical Kinetic Theory, Tyson et al. 1996; Metabolic Theory of Ecology, Brown et al. 2004) may be applied and tested at different levels of organization. Both approaches provide a jumping off point in the endeavor, allow existing data to be leveraged in the identification of frameworks that prove more general. This effort will also aid in the identification of problems with existing frameworks and highlight “holes” in knowledge that need to be filled to both test and improve the framework.

Network and systems theory may be the most valuable starting points based on their successes integrating other types of data across “size” scales. For instance, these approaches already use common phenomena across scales such as rates, flux, and resources, which are similar to the variables used for interaction webs. Further these systems based approaches are already being used in many areas of science, including biology, chemistry, and computer science. However, the current systems-based approaches are typically focused on a particular traditional unit size, rather than investigating how interactions vary across different units and bounds. By applying and adapting current systems-based approaches, challenges in the current frameworks will be identified and can be addressed.

In addition to network and systems theory, there are many examples of conceptual and/or mathematical frameworks that should be evaluated across scales: metapopulation (Hanski and Gilpin, 1991), metacommunity (Leibold and Chase, 2018), ecosystem frameworks describe the interplay of individuals, populations and species across space and time (Odum 1969, Kominoski

et al. 2018). Can these ecological theories be applied to systems at the middle or small scales? In contrast, can the synthetic biology theories surrounding metabolic flux through a pathway (Stephanopoulos, 2012), including mathematical flux analysis (Kim, 2008), and effects of activity/signaling on formation of a (bio)chemical (Vemuri, 2005) be used to describe the interplay between different types of organisms in a community competing for limited resources? Identifying the theories and frameworks currently available to describe biological systems and attempting to generalize them to other scales will provide new insights into both the basic scientific questions and the development of an overarching framework across scales.

4) Identify useful empirical (well-studied) systems from which to develop and evaluate framework(s).

To evaluate both existing and new frameworks, it is imperative that the frameworks be tested with data across all biological scales. However, as collecting data across all scales is very time consuming and challenging, we propose that traditional “model organisms” be used as test subjects for the frameworks. Many of the model systems, including but not limited to well-studied biomolecules and model organisms such as *E. coli*, *Drosophila* spp., *C. elegans*, mice, *Arabidopsis* have decades of data on various processes that range from the *in vitro* atomic/molecular level all the way through multi-organism interactions. Moreover, systems that already serve as important models for questions at larger scales, such as Glanville fritillary butterflies (Hanski 2011), stickleback fish (Barrett et al. 2008), and *Mimulus* spp. flowers (Wu et al. 2008), may serve as important starting points for developing and testing frameworks and expanding the generality of integrated research across scale.

In addition, when the framework is tested on organisms that are not traditional models, we expect that those studies will highlight issues/problems with the framework(s) that are not initially apparent due to selection bias. By identifying the units for which the frameworks scale, we will be able to identify additional units and scales that require further study, broadening the diversity of the unit pool. Extending the number/types of units that are investigated with the framework(s) also will allow for novel predictions regarding the interaction/communication of these new units that can then be tested and lead to advances in our understanding of the biological diversity.

Broader impacts, training/mentorship, courses, institutional structure, etc.:

Addressing the challenge of building and testing frameworks across biological scales will improve links to disciplines outside of biology (e.g., chemistry, physics, math, computer science, epidemiology). This research effort will also attract a wide array of scientists through links to their current research, engaging scientists from all areas of science and arrayed across academia (and outside) to more easily participate in this cross-cutting initiative. An outcome of this participation across fields is the development of (un)conferences, courses, and training programs for the next generation of scientists, ensuring that reintegrated biological problems will continue to be tackled in the future and that efforts to broaden participation in science remain a priority. In addition, these frameworks will demand closer collaborations between scientists

within biological fields and across different fields, helping to integrate traditionally separate disciplines and departments.

How does it reintegrate biology:

Developing framework(s) to describe and predict processes across all biological scales will engage biologists from all sub-disciplines and allow them to approach their own proximate research areas from different perspectives. Furthermore, establishing connections between terms, ideas, and experimental techniques between scales will remove conceptual and communication barriers between biological scientists, helping to reintegrate biology.

Intended Audience:

This white paper is intended for the scientific community. We attempt to make our points accessible to, for instance, graduate students and general science consumers, but acknowledge that some of our examples may require additional information.

References

1. Barrett, R. D., Rogers, S. M., & Schluter, D. 2008. Natural selection on a major armor gene in threespine stickleback. *Science* 322:255-257.
2. Bronfenbrenner, U. 1992. *Ecological Systems Theory*. Jessica Kingsley Publishers.
3. Collins, S.L., Avolio, M.L., Gries, C., Hallett, L.M., Koerner, S.E., La Pierre, K.J., Rypel, A.L., Sokol, E.R., Fey, S.B., Flynn, D.F., Jones, S.K., 2018. Temporal heterogeneity increases with spatial heterogeneity in ecological communities. *Ecology* 99:858-865.
4. Caldarelli, G. 2007. *Scale-free Networks: Complex Webs in Nature and Technology*. Oxford University Press.
5. Hanski, I.A., 2011. Eco-evolutionary spatial dynamics in the Glanville fritillary butterfly. *Proceedings of the National Academy of Sciences*, 108:14397-14404.
6. Hanski, I. A., and M. Gilpin. 1991. "Metapopulation Dynamics: Brief History and Conceptual Domain." *Biological Journal of the Linnean Society* 42:3–16.
7. Kim, H.U., Kim, T.Y., and Lee, S.Y. 2008. Metabolic flux analysis and metabolic engineering of microorganisms. *Molecular BioSystems* 4:113-120.
8. Kominoski, J.S., Gaiser, E.E. Baer, S.G., 2018. Advancing theories of ecosystem development through long-term ecological research. *BioScience* 68:554-562.
9. Leibold, M.A., and J. M. Chase. 2018. *Metacommunity Ecology*. Vol. 59. Princeton University Press.
10. Levin, S. 1992. The problem of pattern and scale in ecology. *Ecology* 73:1943–1967.
11. Odum, E.P. 1969. The strategy of ecosystem development. *Science* 164:262–270.
12. Peters, D.P., Bestelmeyer, B.T. and Turner, M.G., 2007. Cross-scale interactions and changing pattern-process relationships: consequences for system dynamics. *Ecosystems* 10:790-796.
13. Rose, K.C., Graves, R.A., Hansen, W.D., Harvey, B.J., Qiu, J., Wood, S.A., Ziter, C. and Turner, M.G., 2017. Historical foundations and future directions in macrosystems ecology. *Ecology Letters* 20:147-157.

14. Scholes, R. J. 2017. Taking the Mumbo Out of the Jumbo: Progress Towards a Robust Basis for Ecological Scaling. *Ecosystems* 20:4–13.
15. Stephanopoulos, G., 2012. Synthetic Biology and Metabolic Engineering. *ACS Chemical Biology* 1:514-525.
16. Vemuri, G.N. and Aristidou, A.A., 2005. Metabolic Engineering in the -omics Era: Elucidating and Modulating Regulatory Networks. *Microbiology and Molecular Biology Reviews* 69:197-216.
17. Wiens, J. A. 1989. Spatial Scaling in Ecology. *Functional Ecology* 3:385–397.
18. Wu, C. A., Lowry, D. B., Cooley, A. M., Wright, K. M., Lee, Y. W., & Willis, J. H. 2008. *Mimulus* is an emerging model system for the integration of ecological and genomic studies. *Heredity* 100, 220.