Title: Leveraging integrative biology to reveal unexpected interactions in biological systems undergoing environmental change

Authors: Ebony Weems, Noé U. de la Sancha, Carlos Zambrana-Torrelio, Ronaldo P. Ferraris, David C. Blackburn, Laurel J. Anderson.

Summary: We argue that the current environmental changes stressing the Earth's biological systems urgently require study from an integrated perspective in order to reveal unexpected, cross-scale interactions. Such interactions are the basis of a mechanistic understanding for scenarios such as the connections between deforestation and emerging infectious disease, feedbacks between ecosystem disturbance and gut microbiome, and the cross-scale effects of environmental pollutants. These kinds of questions can be answered with existing techniques and data, but we need a concentrated effort to better coordinate studies and datasets from different disciplines to fully leverage their potential.

Introduction/Overview

Over the past decade, the Earth has undergone dramatic environmental changes. Many of these changes are human caused and continue to be a global burden. Large scale, global environmental modifications include climate change, stratospheric ozone depletion, water pollution, urbanization, biodiversity loss, land degradation, and threats to food security. These changes are stressing Earth's complex but delicate biological systems that are unique in the history of the universe and on which human life and health completely depends.

Biologists have been exploring the responses of organisms to environmental change for many years. Traditionally, our scientific training has emphasized tightly controlled, highly focused experiments nested within distinct biological sub-disciplines. These endeavors have been essential to scientific progress and should continue. However, this approach has been insufficient for a full understanding of the range of responses to environmental change that happen in biological systems, whether this is the homeostatic system of an individual organism or an entire ecosystem composed of diverse species. For example, there are significant proportions of plant species studied that have not responded to climate change as predicted by our current knowledge of these species' biology (e.g., Parmesan and Hanley 2015). In human health, complexities in disease response are a subject of continuing research (e.g., Vogt et al. 2016). How can we explain these "unusual" responses? How can we alter biological models to take these phenomena into account? How can integrative biology be used to predict and monitor interactions in models of a range of biological systems?

We posit that many of these unpredictable reactions are based on interactions between biological entities that are unexpected and/or indirect and may represent cross-linkages between scales that have been inadequately explored. We also propose that these interactions can be revealed and more deeply understood through greater leveraging and synthesis of existing tools and expertise that until recently have been siloed in different biological subdisciplines, or in other scientific disciplines such as data science, mathematics and social sciences. We argue that the integration of biology and a commitment to studying biological entities from a systems perspective is essential at this time of environmental upheaval. Our vision is to encourage coordinated teams of biological researchers from different sub-disciplines to work together with a shared goal of describing and quantifying interactions among biological entities within and across scales in order to improve our stewardship of the global environment. Below we outline three examples of pressing research questions linked to human driven-changes in the environment that we believe would benefit from an integrative biology/cross-scale approach.

Question 1: How do the effects of anthropogenic land-use change scale up and down?

Globally one-third to one-half of the land surface has been modified by humans and this is predicted to increase to accommodate the demand for land with growing global populations. Anthropogenic land-use and land-cover change is usually viewed as a large-scale phenomenon. For example, ecosystem fragmentation has received focused attention from ecologists and biogeographers for decades and many effects on biological entities and ecosystem functions have been documented (Haddad et al. 2015). Land-use change influences the distribution and abundance of wildlife species. Changes to host communities can restructure host-pathogen associations, alter abundance and richness, and shape pathogen communities to which humans are exposed. We argue that much more could be learned with an integrated approach that investigates the impacts of land-use change across scales. A key example of the potential benefits of this approach can be found in deforestation.

Most of the biodiversity on the planet is found in tropical forests. Focused studies are still needed for individual species, since we still lack “basic” natural history information for most taxa. However, we argue that assembling data from single species studies fail to demonstrate the cascading effects of deforestation throughout the forest system. An example of these cascading influences starts with edge effects, defined as changes in a population or community structure that can occur in the spaces where multiple habitats intersect. Increased deforestation increases edge effects and results in a series of species-specific impacts. These impacts can be either positive, negative, or neutral (Laurance et al. 2011). Some species go locally extinct other species thrive, resulting in population and biodiversity explosions. Edge introduced species would “normally” not interact with other species in the environment or the environment itself. New interactions create potential novel assemblages and interactions. Among these interactions, there is increased competition for resources and space. Increased competition increases stress levels of organisms, which contributes to immunosuppression and makes species more susceptible to disease or parasites. Increased susceptibility increases the number of sick individuals in forest remnants. Now, more and more people are living closer to forest remnants, creating the perfect storm for increased hotspots for emerging zoonotic and infectious diseases.

Emerging infectious diseases (EIDs) are a key threat to global public health, livestock, wildlife, and overall ecosystem function. The majority of emerging infectious diseases (EIDs) in humans have a zoonotic origin (~ 60%), with most of these (~70%) caused by pathogens originated from wildlife. Different factors have been linked to the emergence of EIDs including socioeconomic and ecological factors. For example, between 31 to 50% of the EIDs since 1940 have been linked to some type of land use change, including deforestation, agricultural intensification, selective logging and other extractive industries. Similarly, vector-borne diseases have also been linked to deforestation including malaria, dengue and Zika virus. Despite their global importance, our knowledge on the distribution, prevalence, and within-host dynamics of a large proportion of potentially pathogenic microbes is limited. There are at least two main hypotheses that may explain disease emergence under global environmental change: 1) the disruption of existing disease dynamics in hosts and pathogen systems (the ‘perturbation’ hypothesis), and 2) the exposure of potential hosts to novel pathogens (the ‘novel pathogen pool’ hypothesis). Both of these hypotheses can potentially further our understanding of increased disease risk and cross-species transmission rates in response to environmental change. An integrated approach is critical to revealing the complex relationships between patterns of deforestation, host organism physiological stress, pathogen burden in the host, and the risk of the pathogen infecting new hosts.

Question 2: How do microbial communities mediate responses to environmental change?

While microbes are microscopic, there are many macroscale factors that shape microbial communities. These factors include climate and topography, land-use, available foods and resources, adaptations of species in the community, species interactions, the arrival and disappearance of species, and physical disturbances. Currently, the ways in which the microbiome is altered by these macroscale changes is not fully understood.

Geography, stress, and host diet have emerged as factors that influence the colonization and success of microbial species in the gut. There are approximately 10-100 trillion commensal bacteria species that comprise the gut microbiome. This number differs across organisms. The interactions amongst these bacteria and their environments is a major driving factor in determining microbial diversity. In these communities a broad range of different interactions exist, ranging from mutualistic and commensal to predatory relationships, and including competition for the same niches. Most of these interbacterial and host bacterial interactions have not been characterized even though they are the subject of intensive studies. These interactions have an immense impact on the host metabolism and physiology. Here we propose two different integrative physiological approaches to understand the effect of environmental change on the interactions between the host and the microbiome.

Microbes primarily derive their nutrients from their environments. Microbes in the human gut derive their nutrients primarily from the host’s consumption of carbohydrates. In response, gut bacteria produce metabolites with various physiological functions. Metabolite production is genus specific and varies with the phyla of bacteria colonizing the area. Diet induced changes in larger organisms often lead to inflammation and increased disease susceptibility. The consequences of these changes in the overall microbiome stability and sustainability is poorly understood. The degree of disease susceptibility due to diet induced changes should also be explored. With an integrated biology approach, the understanding of the physiological linkage between certain plants in herbivores and omnivore diets and organism health could be placed in an ecosystem context to address questions about food webs and organismal health. What are the hidden health consequences for larger organisms of the loss of certain plant species from an ecosystem? How do less diverse diets influenced by environmental change impact organisms and their larger-scale interactions? These kinds of investigations are now possible and important as biodiversity losses in ecosystems accelerate.

Question 3: How does the impact of pollutants on biological systems drive change within and across scales?

Environmental pollutants (microplastics, antibiotics, heavy metals) are well known to have negative effects on biological entities. Epidemiological studies link exposure to environmental pollutants to the development of multiple diseases in single organisms, which has consequences for mortality in populations, and cascading effects in whole ecosystems. However, too many of the studies have been done in isolation and often only at the scales of cells, tissues, and single organisms. The impact of exposure on the health and stability of populations of organisms and their ecosystems are still areas that are unclear. For example, environmentally-induced dysbiosis observed in the gastrointestinal microbiota can be brought on by numerous factors, ranging from inadvertent introduction of non commensal bacteria to dietary alterations to ingestion of synthetic compounds as well as trace metals arising from human activity. In the intestine there is an intimate interaction between microbiota and host cells, that is regulated by chemical signaling. Changes in the chemicals produced can result in major health concerns such as inflammation and metabolic disease. However, the GI microbiota and the interaction with environmental pollutants and the role of these interactions in human health still needs to be studied. Environmental pollutants can also impact food availability and security for many organisms. Changes in food sources can be detrimental to the stability of the Earth's ecosystem. Mapping and predicting the interactions associated with these changes is essential to prevent the loss of biodiversity and the loss of entire ecosystems. This information could also give a more detailed mechanistic perspective on why particular pollutants may be so harmful to ecosystem biodiversity. Such physiological investigations should be paired with larger scale studies of population changes in response to pollution so that the impacts across scales can be fully understood

Integrated Multi-scale Data Repositories

To realize the goal of using integrated biology to predict interactions among organisms, we require data extending from landscapes to organisms to viruses. This approach requires integrating data including large-scale habitat features (e.g., productivity and disturbance) to community composition and distributions of species and their pathogens to patterns of phenotypic and genetic variation within species. While data resources exist for some of these scales of biological organization, it remains arduous to harmonize these heterogeneous data sources due to differing, and sometimes lacking, vocabularies and standards. A vision of a single "data repository to rule them all" is unrealistic but discipline-specific repositories that can cross-talk due to common vocabularies and standards will facilitate discovery across scales of biological organization.

Literature Cited

N. M. Haddad, L. A. Brudvig, J. Clobert, K. F. Davies, A. Gonzalez, R. D. Holt, T. E. Lovejoy, J. O. Sexton, M. P. Austin, C. D. Collins, W. M. Cook, E. I. Damschen, R. M. Ewers, B. L. Foster, C. N. Jenkins, A. J. King, W. F. Laurance, D. J. Levey, C. R. Margules, B. A. Melbourne, A. O. Nicholls, J. L. Orrock, D.-X. Song, J. R. Townshend. 2015. Habitat fragmentation and its lasting impact on Earth's ecosystems. Sci. Adv. 1, e1500052.

Parmesan, C. and M. E. Hanley. 2015. Plants and climate change: complexities and surprises. Annals of Botany 116: 849–864, 2015 doi:10.1093/aob/mcv169, available online at www.aob.oxfordjournals.org

Laurance, W. F., Camargo, J. L., Luizão, R. C., Laurance, S. G., Pimm, S. L., Bruna, E. M., et al. (2011). The fate of Amazonian forest fragments: A 32-year investigation. Biological Conservation, 144, 56–67.

Vogt, Megan B., Anismrita Lahon, Ravi P. Arya, Alexander R. Kneubehl, Jennifer L. Spencer Clinton, Silke Paust, Rebecca Rico-Hesse. Mosquito saliva alone has profound effects on the human immune system. *PLOS Neglected Tropical Diseases*, 2018; 12 (5): e0006439 DOI: 10.1371/journal.pntd.0006439

Brovkin, V., L. Boysen, V.K. Arora, J.P. Boisier, P. Cadule, L. Chini, M. Claussen, P. Friedlingstein, V. Gayler, B.J. van den Hurk, G.C. Hurtt, C.D. Jones, E. Kato, N. de Noblet-Ducoudré, F. Pacifico, J. Pongratz, and M. Weiss, 2013: Effect of Anthropogenic Land-Use and Land-Cover Changes on Climate and Land Carbon Storage in CMIP5 Projections for the Twenty-First Century. J. Climate, 26, 6859–6881, https://doi.org/10.1175/JCLI-D-12-00623.1