Centering microbes in the emerging role of integrative biology in understanding environmental change

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Running title: **Microbes and integrative biology for environmental change**

Synopsis: We argue that the current environmental changes stressing the Earth's biological systems urgently require study from an integrated perspective to reveal unexpected, cross-scale interactions, particularly between microbes and macroscale phenomena. Such interactions are the basis of a mechanistic understanding of the important connections between deforestation and emerging infectious disease, feedback between ecosystem disturbance and the gut microbiome, and the cross-scale effects of environmental pollutants. These kinds of questions can be answered with existing techniques and data, but a concerted effort is necessary to better coordinate studies and data sets from different disciplines to fully leverage their potential.

Introduction

Our planet has undergone dramatic, global anthropogenic environmental changes (Haddad et al. 2015). These include climate change, habitat fragmentation and loss, accelerated land use change and degradation, urbanization, biodiversity loss, and threats to food security (Haddad et al. 2015, Richardson et al. 2018, Raza et al. 2019). We are now witnessing increasing stress on Earth's complex but delicate biological systems on which human life depends (Otto et al. 2017, Frolicher et al. 2018, Archibald et al. 2018). Biological responses to anthropogenic environmental change have been a major focus for researchers across disciplines (Walther et al. 2002, Peck et al. 2011, Radchuk et al. 2019) and scientific training has emphasized specialization within these disciplines. These focused studies are essential to scientific progress and should continue. However, many responses cannot be adequately studied by viewing them through a single disciplinary lens because of the complexity of ecological systems and interactions that often cross boundaries of spatiotemporal scales or biological organization levels (Figure 1). A timely example is the influence of environmental change on the emergence and spread of infectious diseases across scales (Vogt et al. 2018). The current global COVID-19 pandemic reveals the need for transformative change in the way we interact with our environment (Daszak et al. 2020, Barouki et al. 2021). This is the ultimate example of cross-scale dynamics, because the physiologies and behaviors of individual organisms and their pathogens cascade upwards to influence population to community to landscape and even biosphere level relationships (Figure 1).

In this paper, we call attention to the importance of cross-scale interactions in the context of global environmental change, particularly the linkages between microbial activities at the microscale level and a range of macroscale phenomena. We posit that many "unusual" responses to environmental change 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. The nature of these interactions can be revealed and better understood through a synthesis of tools and expertise that traditionally has been siloed into different scientific disciplines across biology, data science, mathematics, and the social sciences. Our vision is to encourage coordinated teams of researchers representing different biological scales to work together with a shared goal of describing and quantifying interactions within and across biological systems within and across scales. Here, we outline approaches to address pressing research questions linked to anthropogenic-driven changes in the environment that we believe would benefit from an integrative biology or a cross-scale approach. Our work focuses on microbial phenomena as potential drivers or mediators of macroscale phenomena and provides three concrete examples: 1) interactions between the gut microbiome and the host's external environment; 2) the large-scale distribution of plants and their connection to soil microbial communities, and 3) the links between infectious diseases and environmental disturbance.

The importance of microbes

Microorganisms support the existence of all trophic life forms (Cavicchioli et al. 2019). They influence the organization of communities (e.g. composition), and affect biogeochemical cycles and ecosystem dynamics (Paez-Espino et al. 2016, Henson et al. 2017). Yet, microbes cannot be easily seen, are highly abundant, difficult to quantify, and are known to be influenced and influence various macroscale factors. Climate and topography, land-use, available resources, colonization, and physical disturbances impact the ecological microbial diversity, distribution, and abundance (van Leeuwen et al. 2017, Bissett et al. 2013, Wu et al. 2018, Turley et al. 2020). Currently, the ways in which microbial communities influence macroscale changes are not fully understood. Nor do we have a complete grasp of the cascade of changes that occur at larger scales when microbial physiology, community composition, and distributions shift. This is where greater integration of biological research across spatial scales is of critical importance. Understanding the role of microorganisms is essential to predict, manage, and mitigate the major challenges facing the environment today.

Example 1: Connecting changes in the gut microbiota to larger scales

Human gut bacteria derive their nutrients primarily from host's consumption of carbohydrates producing metabolites that support various physiological functions, including maintenance of the gut barrier and immune modulation (Belkaid et al. 2014, Singh et al. 2017). This symbiotic relationship between gut microbiota and host can be altered, resulting in dysbiosis, an abnormal composition of bacteria colonizing the gut, that can be detrimental to the host. However, the larger-scale, ecological factors that alter the overall stability and sustainability of the gut microbiota have been less studied.

What can bring about environmentally induced dysbiosis? Different studies have shown how interbacterial and host:bacteria interactions may regulate this delicate balance among bacterial species in the gut microbiota (Rosenfield 2017, Leon-Coria 2020). Composition of gut bacteria is known to differ markedly between populations consuming different types of foods. Recently bacteria in fecal samples of African children were found to be comprised mostly of genera belonging to *Prevotella* and *Xylanibacer* of the phylum Bacteroidetes whereas those in European children belong to *Acetitomaculum* and *Faecalibacterium* of the phylum Firmicutes (De Filippo et al 2010). Food security and nutrition, exacerbated by climate change and human conflict (e.g. wars, immigration), are key elements altering the gut bacteria. For example, climate change alters the types of crops produced by farming activity would be expected to result in dietary alterations that will dramatically impact the gut microbiota composition. Exposure to environmental contaminants can also alter the gut microbiota in the gastrointestinal (GI) tract of vertebrates. Some of these contaminants can compete with microbiota-derived ligands for host receptors interacting with commensal microbiota, leading to dysbiosis that, if chronic, can result in inflammation of the digestive tract and in the onset of inflammation-induced diseases (Petriello et al 2018). For example, signaling pathways linked to the intestinal aryl hydrocarbon receptor (AHR), which is normally regulated by gut microbiota-derived indoles to maintain gut homeostasis, can instead cause increased intestinal inflammation as a result of exposure to environmental contaminants like polycyclic aromatic hydrocarbons and polychlorinated dioxins which can also bind to the AHR (Hashimoto et al. 2012, Kim et al. 2010, Nikolaus et al. 2016). Therefore, external environmental stresses can result in changes in the gut microbiota, that if dysbiotic, can eventually lead to major health concerns such as inflammatory and metabolic diseases.

Since different gut bacteria synthesize and secrete different metabolites, its production has become an excellent tool to measure and monitor bacterial composition and possible relationships between biological marker levels and stressors (Aguirre-Becerra et al, 2021). Biomarkers represent responses which may be functional or physiological, biochemical, or a molecular interaction (WHO 1993) and are widely used as predictors of the health of individual organisms. Environmental metabolomics has emerged in recent years as a tool to study the interaction of organisms with their environment (Morrison et al. 2007, Bonvallot et al. 2018). Recently metabolomic studies were used to identify stress arising from environmental temperature shifts on various whole animal models (Schulte 2015, Shamloo et al. 2017). The altered metabolites that indicate stress may have been synthesized by the host, by the microbiota associated with the host, or by host: microbiota interactions. Altered gene expression in bacteria exposed to heat and organic pollutants (Ye et al. 2012) can also potentially yield altered levels of metabolites acting as stress biomarkers. The information that links changes in metabolites to changes in microbiota 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 and other stressors to fully understand the impacts across scales.

Recent improvements in computational speeds, memory, and user competence have allowed for a new generation of computer scientists and a rise in computational proficiency and modeling. Computational models are an important integrative tool used to illustrate the microbe-based molecular mechanisms characterizing and underlying interactions of organisms. For example, computational models were developed to investigate the functional association between the human host and the gut microbiota (Ma et al. 2007) and to explore the interactions between bacteria in the gut ecosystem using genome scale metabolic models (Shoaie et al. 2014). Integration of functional metabolic models and clinical data can elucidate the linkage between organism health and microbial ecosystems. These approaches can also be used to study the influence of environmental change on disease onset and progression in organisms (Figure 1). An integrated biology approach can be used to understand the physiological linkage between gut microbiota in both herbivore and omnivore diets. This could be scaled up to place organism health in an ecosystem context to understand how altered food webs (Morris et al., 2016) affect individual health via alterations in the gut microbiota and the metabolites they produce.

Example 2: Microbe-plant interactions across scales

Interactions between plants and microbes have been intensively studied and the influence of mycorrhizal symbioses and local soil fertility on individual plant fitness is well known and documented by numerous studies. However, examinations of the distribution of soil microbes at larger scales are more recent and reveal intriguing patterns relative to plant distributions that require further exploration. Fierer and Jackson (2006) investigated the biodiversity of soil bacterial communities at continental scales and found that diversity was most strongly related to soil pH and was not correlated with regional plant species diversity. Soil fungal communities have been shown to respond to habitat fragmentation, with soil legacy effects persisting from fragmentation of ancient forest sites in some cases (Grilli et al. 2017, Mennicken et al. 2020). This work raises an important reminder that environmental changes that drive spatial plant diversity patterns may or may not drive microbial diversity patterns at larger scales.

Invasion ecology has uncovered important interactions between soil microbes and invasive plant species, suggesting that invaders change soil microbial communities to benefit themselves (Klironomos et al. 2002, Callaway et al. 2004) and noting that microbes are responsive to changes in leaf litter that come with new plant species entering the community (Ehrenfeld 2003). Yet, uncertainty remains regarding whether invasive plants alter soil microbes quickly enough and over large enough spaces to affect invader spread (Levine et al. 2006). Field studies remain rare relative to lab studies and more could be discovered regarding how interactions between plants and microbes vary in different environmental contexts (van der Putten et al. 2013). The proximity of other plant species, variations in weather conditions, and soil resource availability may all affect how strongly the microbial community interacts with plants in a certain site (Bennet and Klironomos 2018). While soil microbes, particularly mycorrhizal fungi, are known to be important in soil restoration efforts, benefits of soil microbe additions or amendments vary across sites (Harris 2009). These plot level effects are nested within the broader context of regional climate, soil and biome types. Are some of the unpredictable responses of plants to climate change (Parmesan and Hanely 2015) caused by interactions with microbes that are highly local and site specific? The research community is moving toward answering these questions, but more extensive cooperation is needed between biologists who study microbial physiology and soil microbial diversity with molecular approaches and field biologists who study whole plants, plant populations, plant function within ecosystems, and plant spatial distributions.

Example 3: Impact of land-use change on disease emergence

Zoonotic diseases, those transmitted from animals to humans, include viruses such as HIV/AIDS, MERS-CoV, Ebola virus, and H1N1, swine flu, and rabies (Jonsson et al. 2010, Ogden and Gachon 2019, El-Sayed and Kamel 2020), and other endemic pathogens such as West Nile virus. Globally these diseases cause close to a billion human cases, and millions of deaths every year (Karesh et al. 2012) and represent a burden to global public health, livestock, wildlife, economy, and overall ecosystem function. Emerging infectious diseases (EIDs, e.g. SARS-CoV) are usually the result of environmental change (Figure 1). For example, land use change (deforestation, agricultural expansion, and habitat fragmentation) is a significant driver of the emergence, spread and transmission of infectious diseases, accounting for over 30% of the spillover events since 1940 (Sehgal 2010, Loh et al. 2015). An integrated approach is critical to elucidate 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 due to diet induced changes to microbiome composition. Individual determinants of spillover should not be studied in the isolation of specialized disciplines. An understanding of the bacteria-host-virus interaction is critical to predict spillover events in at risk communities. Translational models that integrate data from experiments, epidemiological studies, and field studies would elucidate the relationships of these determinants. For example, modeling spatial interactions between organisms and integrating life history traits into disease ecology is vital to support operational platforms that can be used for risk analysis, preparedness, surveillance, and control (Lambin et al. 2010, Carroll et al. 2018, Valenzuela-Sánchez et al. 2021).

Globally, one-third to one-half of the land surface has been modified by humans (FAO 2015) and likely to increase to accommodate the demand for land with growing global human populations. Land-use change influences the distribution and abundance of animal, plant, and microbial species in the environment and in host species (Debinski et al. 2000, Holt and Keitt 2005, Fahrig 2017). Recently, microbiome comparison of birds in primary forest vs coffee monoculture showed shifts in microbial communities as a consequence of habitat type changes (San Juan et al. 2020). Changes to host communities, including habitat fragmentation, can restructure host-pathogen associations, alter abundance and richness, and shape pathogen communities to which humans are exposed (Brooks et al. 2014, Gibb et al. 2020) primarily through edge effects. Edge effects are changes in a population or community structure that occur in spaces where multiple habitats intersect (Ries et al. 2004, Pfeifer et al. 2017) resulting in a series of species-specific impacts (Laurance et al. 2011) that can be positive, negative, or neutral (Ewers & Didham 2006, de la Sancha 2014). Edge habitats allow for novel species interactions that create potential novel assemblages and interactions among wildlife, free range livestock, and also humans (Figure 1, Deem et al. 2001), as well as physiological changes in individuals. Stress caused by increased competition for resources and space may lead to immunosuppression for wildlife in disturbed habitats (Acevedo-Whitehouse and Duffus 2014). For example, smaller forest remnants have shown evidence of increased stress hormone (glucocorticoids such as cortisol or corticosterone) levels in small mammals (Meddings and Swain 2000, Boyle et al. 2021), although this effect varies across taxa (Ordóñez-Gómez et al. 2016, Rimbach et al. 2013). Increased stress levels in organisms contribute to immunosuppression and makes species more susceptible to viruses, bacterial infections, or parasites (Brearley et al. 2012, Acevedo-Whitehouse and Duffus 2014) and changes in the host microbiome (Hernandez et al. 2021) and potentially epigenetic effects (Chatterjee et al. 2018). We argue that much more could be learned with an integrated and information-driven approach that investigates the impact of land-use change on environmental microbiota and microbial function across trophic levels.

Habitat fragmentation has also shown to increase poaching and hunting through both legal and illegal harvesting of fauna (Tensen 2016, Allen et al. 2017). These animals are consumed for sustenance or end up in markets as consumables, or as part of the pet trade. Dramatically increasing the probability of disease incidence (Watsa et al. 2020). With increased population growth, widespread land-use change, and deforestation, more people are living closer to forest remnants. Possibly creating the perfect storm for increased hotspots for emerging zoonotic and infectious diseases (Loh et al. 2015, Gibb 2020). The onset of the coronavirus pandemic in late 2019 was not unexpected considering, increased population growth and urbanization, habitat destruction, globalization of animal trade, and intensive farming, all increasing the transmission of zoonotic pathogens and infectious agents (Plowright et al. 2017). Despite their global importance, our knowledge on the distribution, prevalence, and within-host dynamics of a large proportion of potentially pathogenic microbes is limited. How these factors interact and how biological barriers to infection function are questions that will help scientists predict and prevent spillover events in the future.

Conclusion

How do we integrate biology? Some studies have started to explore and understand the diverse roles of the microbial world in driving and interacting with macroscale phenomena. Excellent examples of this work are showcased above. However, we argue that this integrative approach is rare in the biological sciences. Many hindrances, including time and flexibility have created barriers to collaboration. In our siloed research system, a microbiologist may find it easier to collaborate with a biochemist than a landscape ecologist or a social scientist. How do we foster and support the more unusual collaborative linkages that are needed to understand the complexities of our changing environment? Integration can be fostered through the collection, processing, and application of data, extending from landscapes to organisms to microbes. Data collected would be beneficial to understand large-scale habitat features (e.g., productivity and disturbance) to community composition, multiple dimensions of biodiversity (e.g., taxonomic, functional, and phylogenetic), to patterns of phenotypic and genetic variation within species (Miraldo et al. 2016, de la Sancha et al. 2017, 2020), their level of stress, and distribution of species and their micro and macro parasites.

Integrative collaboration sites and institutes such as the NSF supported National Ecological Observatory Network (NEON) and the National Socio-Environmental Synthesis Center (SESYNC) are essential to the fostering of scientific exchange and collaborative efforts amongst experts from various backgrounds and disciplines. NEON is a place-based, multi-scale data collection effort where diverse data streams are being collected on the same site. NEON Core Sites could serve as collaboration hubs where people from diverse biological fields could come together to discuss potential joint projects and be encouraged to think beyond the single site scale as well. SESYNC encourages researchers from both the natural and behavioral sciences to collaborate in an effort to share approaches to address many of the environmental challenges impacting our globe. Research Coordination Networks with interdisciplinary themes could also facilitate integration.

Natural history collections and other biological repositories are becoming directly important for understanding the biodiversity, biomedical research, the effects of anthropogenic and climate changes, zoonotic hotspots, and conservation management (Tewksbury et al. 2014, Galbreath et al. 2019, Cook et al. 2020, Thompson et al. 2021). In addition, there is increased need to develop and maintain international repositories (Colella et al. 2020). Both physical and virtual repositories that are integrated with virtual biodiversity data would benefit researchers across disciplines. For example, Arctos, Atlas of Living, SpeciesLink, iDigBio, and VetNet provide data used across disciplines (Cook et al. 2020). Additionally, in order to improve the modeling of systems, natural history collections should be coupled with readily available high- resolution imagery to help improve description of anthropogenic biomes or anthromes through space and shorter time intervals (de la Sancha et al. 2017). As high-resolution imagery utilization was recently demonstrated to considerably improve land cover patterns in forest and land used for food productivity in highly disturbed habitats and connectivity (Boyle et al. 2014, Findell et al. 2017).

In educational settings, multi-faceted problem-based learning and cross discipline curriculum could support multi-scale and multi-perspective thinking in students. In this way, people can learn the tools and perspectives that different disciplines contribute to solving complex problems. This highlights another tension between teaching skills vs. content. Arguably, a content emphasis encourages the siloed approach while teaching skills that presumably transfer across settings encourages integration. Incentivized faculty/teacher collaboration and learning cohorts would be beneficial to the development and implementation of multi-discipline curriculum and project design.

It is also important to acknowledge that integration has become easier as electronic collaboration tools for writing and sharing data, code, and images have increased. Some of the scientific community's "unwillingness" to collaborate in the past may simply have been due to the barriers to quickly sharing documents and communicating across large spaces. The COVID-19 pandemic may catalyze another wave of integrative work by making the virtual workspace more normal and increasing accessibility of meetings and conversations to colleagues who could not previously participate due to travel and funding constraints. At the same time, high speed internet access should not yet be assumed, particularly for students and low-income countries, and ensuring equitable access to the tools and training necessary for powerful scientific collaboration in the 21st century is essential.

In summary, we have highlighted a range of research examples that connect the microbial world to the macroscale. We encourage this work to continue and expand. The mechanisms that drive large scale patterns may be working at smaller scales than some macroscale biologists realize, and different environmental drivers may operate at different scales. In our rapidly changing environment, we cannot afford to overlook these details.

Figure 1. Conceptual framework identifying key components of the ecological hierarchy linking: 1. Individuals of a particular taxa and the various attributes with additional datasets associated (e.g., voucher specimens, their associated tissue samples, DNA samples, skeletal material, associated parasites (ie. endoparasite, ectoparasites, blood parasites, and viruses), microbiomes (e.g., gut, skin, fecal), and dataset from hair samples (ie. stress hormone, isotope profiles, metabolites, disease prevalence and parasite loads). 2. Population's dynamics and 3. Community structure, quantifying various dimensions of biodiversity (e.g., TD, FD, and PD), and potential changes along gradients. Population and community structure should be coupled with 4. Ecosystem and 5. Landscape level datasets to understand the impact that human driven environmental change impacts their structure. Finally, landscape level modeling can be valuable for inference and modeling of even bigger picture analyses at the 6. Biosphere level as we assess the interplay between local, regional and landscape level processes and biodiversity patterns react to global changes (e.g., climate change). Phylogeny was constructed using Steppan and Schenk (2017) beast concatenated dataset. Figure was created on BioRender.com.

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