Perturbation Research Teams Using Reintegrated Biology (PeRTURB)

Understanding the response to extrinsic perturbations across scales and systems: Creating a framework for collaboration across scales.

Group members

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The Goal:

We would like to understand the impacts of extrinsic perturbations across scales, time, and systems. Comparing similar systems that do and do not change upon perturbation will give measures of robustness and resilience vs. response/adaptation. The difference in response can help us understand the system and where there is amplification and buffering of perturbations or stimuli. We hope to identify knowledge gaps and create a framework to link resources and expertise/groups asking the same question at different levels and in different biological contexts.

We will address our goal by analyzing two scales of biological systems:

1) **From genotype to phenotype**

2) **From organism to ecosystem**

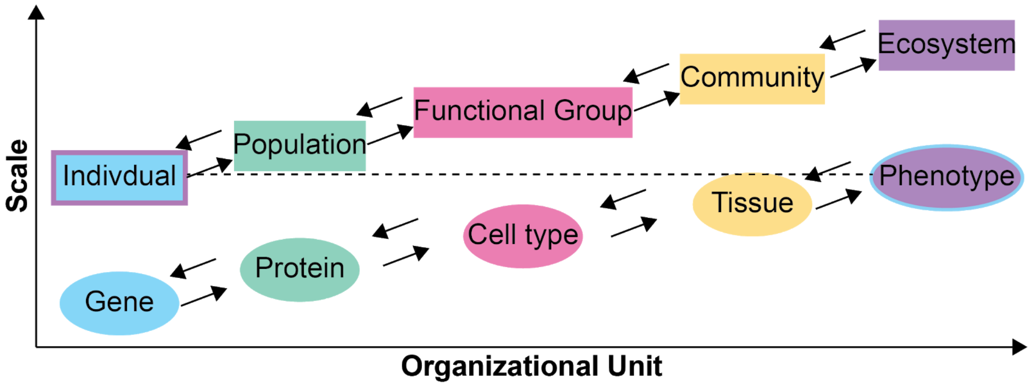

Figure 1. Diagram demonstrating the multi-level investigation strategy. At smaller scales, a traditional strategy will be used to identify the genetic or molecular causes of perturbation-induced phenotypes at the individual level (bottom up). Small scale experiments will follow identification of pertinent questions after natural perturbations are discovered. In larger scale investigations, the organizational unit starts at the individual with the potential to scale to whole ecosystems. Large scale investigations will identify perturbations present in the ecosystem that affect populations or individuals (top down).

WHAT

Here we define an extrinsic perturbation as an external factor that alters the function of a biological system such as environmental changes, infectious diseases, drug inhibition, genetic manipulations (Wang 2013).

The overarching goal of this vision paper is to create a framework that allows connection between scientists engaged in multiple scientific disciplines, but that are asking related questions around perturbations in their biological systems. Field data exist that describe extrinsic environmental changes in water, temperature, and air caused by climate change, pollution, wildfires, etc., and these changes are correlated with relevant ecological, evolutionary, agricultural, and health-related issues. However, there is a lack of connection between the scientists and community members, and a severe gap in the transferable knowledge bases, which prevents solving the problems that arise. There is an acute need to use the available data to understand the systems in question. We propose to create a digital and hands-on framework that allows for connectivity between people, data, resources, training, and tools to address this problem.

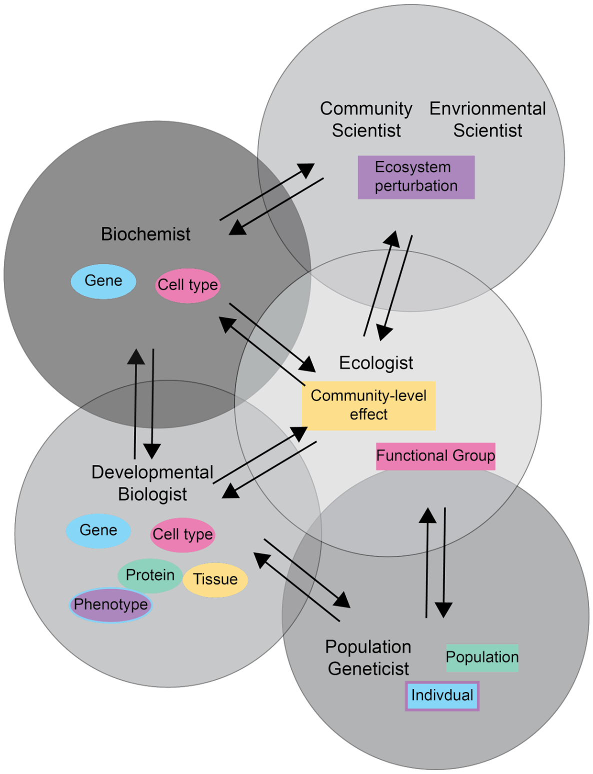

Figure 2. Example of reintegration of disciplines towards a single objective. An ecologist identifies population declines in their organisms of interest which may be caused by an extrinsic perturbations. The ecologist has worked with an environmental scientist to identify possible drivers of these changes. Water analysis identified 5 toxins in excess concentrations in the ground-water in the area that may be leading to the population decline. Using this framework they identify a biochemist to define the molecular functions of these toxins and a developmental biologist to determine the effects of these toxins on developing embryos. Linking their datasets using an open-access format, the developmental biologist identifies concentrations of 2 toxins that create morphological developmental defects. The biochemist identifies protein structures and

molecular pathways that the toxin affects. The developmental biologist is then able to test the changes in expression of the factors in these pathways *in vivo*. They determine that there is one specific pathway that causes the morphological defects. The ecologist then initiates population-level and ecotoxicological studies of this and other populations to link the effect of both the direct (via the pathway identified above; e.g., stunted growth) and indirect effects (via as of yet, unidentified pathways; e.g., decreased reproductive function) of toxin levels on population demographic parameters. Identified indirect effects of toxins (unidentified pathways) represent opportunities for additional mechanistic exploration at lower levels of organization (e.g., molecular).

The potential impact of PeRTURB is threefold. First, PeRTURB has the potential to redefine the current experimental research paradigms by creating opportunities to collaborate in new areas spanning multiple space and time scales by allowing groups from different fields and types of institutions who use different research models to answer pertinent questions regarding environmental changes and system responses. Second, to work together in a meaningful way, collaborative groups will have to push the limits of current research boundaries, inherently creating innovation. Third, the collaboration and innovation will not only enhance scientific discovery, it has the potential to impact environmental justice, education, and outreach initiatives by including stakeholders from multiple populations.

- Parameters:
  Scientific problems being studied will help PeRTURB determine and define many of the parameters, however, some of the following parameters provide a modeling framework that cuts across scales and projects:
    - Define extrinsic vs. intrinsic perturbations in a system of interest and then distinguish their effects in that system’s output.
    - Determine the size of perturbations and normalize their corresponding effects at different length/time scales.
    - What are the system factors that serve as Amplifiers and buffers/silencers of perturbations?
    - What is the role of system complexity as a modulator of perturbation effects?

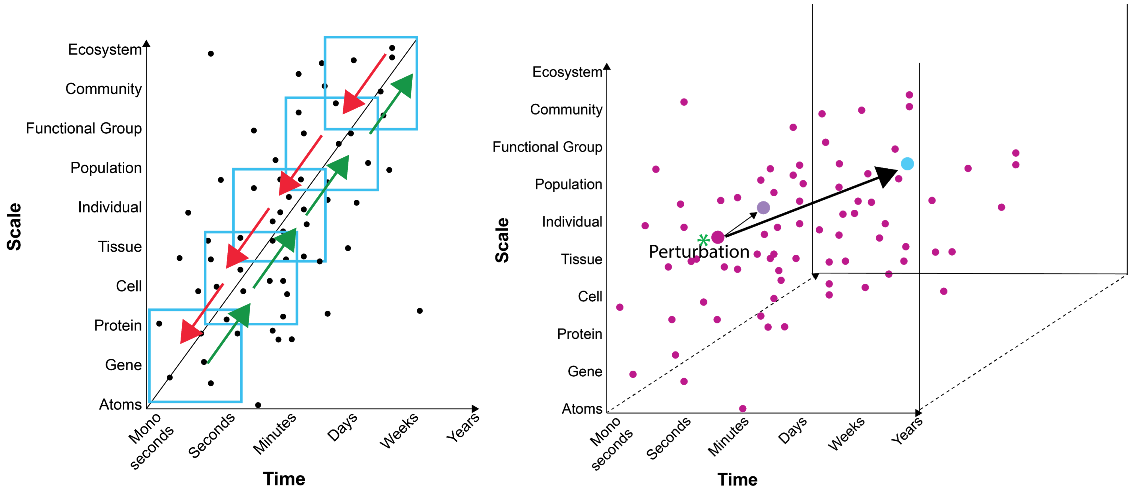

Figure 3. Diagram of the multiple scale and time traversed by biological systems. Points on the scale represent important components of one large system. The left panel shows the length and time scales spanned by different research areas as distinct rectangles. The red and green arrows show the cross-disciplinary research endeavours that will bridge fields within the Supergroup. The right panel shows perturbation as a third dimension whose effect will be felt across all scales, independent of the level in which it originated. One example perturbation is shown (arrows). Two possible outcomes for the same perturbation are shown, depending on the resiliency of the system. Arrow length and thickness indicate magnitude of change. One goal is to create a standardized metric to measure variations away from the mean between populations.

WHY

Approaches to research in biology have led to fragmentation into sub-disciplines. This has been beneficial for advancing knowledge, especially with the tools available up to the present. Many “silo-ed” systems of extrinsic perturbation/change have been studied at one scale or another, but very few have been tackled by one supergroup across vast scales. Some examples that cross scales include the NSF NEON project (www.neonscience.org) and the Physiome Project (www.physiomeproject.org). The current state of technology offers opportunities for expanding these approaches to massive, coordinated, real-time collaboration (internet, data-sharing, data collection, cloud computing and sharing, statistical tools, …). A project based on an identified environmental problem that needs to be understood at the molecular, cellular, developmental, population, and ecosystem levels can harness these opportunities.

Creation of supergroups researching one topic on multiple scales, creating a super-discipline, is an ambitious goal that currently has few template examples. Yet, there is great potential for development of research teams that use new scientific language that spans scales, spoken by researchers in disparate fields. There is an added potential to offer training across these vast scales, educating new generations of scientists who know no other way of approaching a project than by expecting this trans-disciplinary communication and research effort.

Human-caused environmental change is a pressing problem and requires frameworks to approach the current challenges of understanding and addressing these changes. We envision projects with an environmental toxicology “perturbation” as highly appropriate within the framework that we describe in this paper. Tackling these problems would provide tangible positive impact to the affected populations and would help meet the challenges of creating a sustainable future for humans and other life on the planet.

HOW

Effectively understanding the cross-scale impacts of perturbations on biological systems will require researchers to build collaborations across disciplines, integrating a variety of scale-specific approaches, unified under a common analytical framework.

Establishing this framework will be critical to the success of such a project, and begins with the planning stages of the project. The cross-scale nature of this work means that research output from one group will be used as inputs by another. This chain of dependencies means that communication among groups regarding research needs will be an ongoing and evolving processes throughout the life of a project. System-agnostic metrics will be necessary to generalize the impact of a perturbation across these levels of organization. Baseline variability of extrinsic impacts (e.g., the condition that is perturbing the system) could be used as a way to scale the impact of a given perturbation (for instance, as the number of standard deviations away from the mean of that perturbing condition).

While many of the methods and techniques used to address these questions will be specific to a particular level of biological organization (e.g., gene regulatory networks, reaction-diffusion models, population models linking phenotypic responses of perturbations to demographics), a generalizable pipeline could be developed to facilitate the integration of research outputs from these different approaches. Two aspects in particular will be critical, 1) propagating uncertainty across the dependent analyses, and 2) exploring the direct vs. indirect effects of a given perturbation on the dynamics at a given level of organization. A hierarchical Bayesian modeling approach can be used to effectively quantify the degree of parameter uncertainty for each analysis, and account for this uncertainty in downstream analyses. The direct vs. indirect effects of a perturbation could be estimated within this analytical framework, similar to the approaches used by structural equations models.

Once relationships among different parameters of interest are estimated, simulations could be used to explore the outcomes of different perturbation ‘scenarios’. Uncertainty in these estimated relationships could be integrated into these forecasts and has implications for both basic and applied research efforts.

However, a number of barriers exist in effectively implementing such a project, both systemic and research-related. Perhaps of most importance is the ability to find a common framework to analyze, model, and discuss research findings across scales. Biological systems are complex, and researchers often have a limited scope of knowledge of the components of the system, most of which interact nonlinearly, and the kinetics of those interactions are largely unknown. Nonlinearity means systems are not static but are instead dynamic and change over time. Therefore, longitudinal data at all scales will be key. The collection of these data alone may require substantial laboratory- and field-based efforts. While some data derived from previous research efforts may prove fruitful, as it stands now, there is a lack of incentive for researchers to share unpublished results or raw data.

To make matters more complicated, systems often have redundant components that maintain the activity of the system when another component malfunctions. Biological redundancy can often only be identified after functional experimentation. These parameters of biological systems pose a problem for researchers that may be working at vastly different scales (molecular to ecosystem) hoping to integrate their disciplines. Thus, normalization of data (component interactions, system phenotype, strength of perturbation, and time) are inevitably required to integrate. These data could subsequently be placed into a general system models such as ordinary differential equation (ODE) models. ODEs have been used successfully to understand homeostasis and disease manifestation. The hope for building a general model is to help predict future experimental outcomes and elucidate commonalities of resilient systems at multiple scales of biology.

Systemic barriers, which often reach across a number of projects. These include improving training and mentoring for scientists at all career-levels. This training might focus on everything from exposure to different scientific fields of research, to quantitative analysis, to science communication (as one of the major challenges in working across disciplines is effective communication). Opportunities for researchers to connect across disparate disciplines to develop projects and build collaborations are lacking. The traditional structure of academic research does little to connect researchers across scales. Funding organizations could encourage this long-term cross-scale work through the organization of workshops and funding opportunities.

BROADER IMPACTS

PeRTURB will allow for broader reach within scientific communities and the greater society by creating connections between distinct disciplines related by research questions in an open access and collaboration-friendly manner. In addition, communities with limited resources will be able to participate in PeRTURB at multiple levels. The intention is to bring together a diverse set of researchers, from community scientists to those at research-intensive institutions to accomplish shared goals. A wide variety of disciplines could be represented, including, *Chemistry, Genomics, Biochemistry, Microbiology, Molecular and Cell Biology, Developmental Biology, Physiology, Population Ecology, Community Ecology, Ecosystem Ecology,* *Environmental Biology, Epidemiology, Endocrinology, Population Genetics, Bioinformatics and Statistics*.

Labs will have the option to host trainees for super-disciplinary training opportunities that may span longer timeframes from traditional training periods. The training goals include producing super-disciplinary biologists that have focused on a single system across vast scales. Ultimately, collaborative networks create opportunities for trainees with regard to additional options for future training and employment.

PeRTURB projects will engage all of the “silos” within Biology to focus on a single object, achieving a re-integration of Biology and drawing in outside fields such as computer modeling, chemistry, environmental science.

Conclusion

Biological systems are shaped by extrinsic perturbations across multiple scales. To address the complexity of the response to perturbations across systems we propose the creation PeRTURB, a framework that aims to connect scientists engaged in multiple disciplines. PeRTURB has the potential to address knowledge gaps and reintegrate different fields of biology.

References

Wang RS. (2013) Perturbation. In: Dubitzky W., Wolkenhauer O., Cho KH., Yokota H. (eds) Encyclopedia of Systems Biology. Springer, New York, NY

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