

## How do processes interact across levels of biological organization?

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**Thesis:** Biological systems are organized in a size-hierarchy, from sub-molecular, via cells, tissues, and organisms to ecosystems and biomes. Different entities within each level of organization interact at varying spatial and temporal scales, and their interactions determine static as well as dynamic properties of the system. However, interactions occurring within a given level influence, and are influenced by, interactions that occur at many other levels of organization, and these together determine the emergent properties of biological systems. For example, the introduction of rabbits to Australia and sub-Antarctic islands in the 1800s had cascading effects across multiple scales throughout the ecosystem [1]. Similarly, but at different scales, muscle stretch injury has cascading effects that, in combination with organismal behavior, environmental factors [2], and drug therapies might determine the susceptibility of muscle once recovered to re-injury [3]. Such examples illustrate the complex cascading effects of cross-level interactions that occur up and down levels of biological organization. Improved understanding of complex interactions among levels would facilitate predictions with better accuracy of wide-scale effects that result from relatively simple perturbations at a single level (e.g. an injury, a simple mutation, a species introduction). Given our capacity for complex modeling and the explosion of big data science usually used within each level of biological organization, the time has come to push for the integration of these methods to provide more nuanced modeling of cascading interactions across levels of biological organization.

**Big question and exciting science:** Tackling questions at the *Rules-of-Life* level through collaborative, convergence-science approaches can mitigate the common problem in single-discipline science that strong patterns in the data are mechanistically inexplicable, an outcome caused by changes at organizational level(s) that are not covered by the disciplines' tools. For example, muscle stretch-injury causes contractile functional changes that cannot be explained without molecular level insight from RNA-seq that can establish the cascades of up/down molecular signal regulation following injury. It follows that convergence-science approaches are better at integrating data from across levels to more robustly capture otherwise unquantifiable relationships between form, function, and mechanics, within and across systems.

Beyond “static” appraisals at single levels, we currently lack robust understanding of connections among levels and systems. For instance, most complex network analyses still only cover single (e.g. molecular, cellular) levels, leaving details about connections among levels, including their strength, direction, and feedback/forward nature, poorly understood.

How do we begin to tackle this problem? First, we propose that workers investigate relatively simple systems, with manageable complexity of interactions across few levels of organization (e.g. protein interactions within single cells). This may help train network analysis and Artificial Intelligence (AI) algorithms to scale across levels. Second, classical “model” organisms (e.g. *C. elegans*, *Danio rerio*) will allow us to capitalize on sparse data at single levels with data existing across levels to further train algorithms. Third, suites of algorithms can be bench-marked on classically challenging systems, like muscle or the savanna ecosystem. Fourth, moving on from steady-state systems, predictive analysis approaches can be developed to tackle truly complex systems, such as environmental change (in a cell, or across the planet), where innumerable feed-back loops currently compound our ability to draw conclusions that could inform policy-making, governance, and emergency preparedness. Moving on, applications will extend to more accurate/effective manipulation of environment, food, and health, to prediction of population susceptibility, and to responses of systems to injury, illness, and aging.

**The potential impact:** An understanding of how processes interact across levels of biological organization allows for better predictions of biological system responses to perturbations across levels (both predicting system responses when perturbations occur at low(er) levels, and how perturbations at higher levels influence responses at lower levels). Establishing the strength and direction of linear as well as non-linear pathways between levels will provide better predictive power to models of feedback within networks at any given level. Combined with integrating scalability between systems and levels, the defined strength of inter-network connectivity may be more fluid with similar nodes of cross interaction. When appropriately identified this should reduce noise within network connections and strengthen the predictive ability of models across and within levels. The strength of such systems is the ability to understand impacts across widely-separated levels such as understanding the impacts of climate change down to the cellular level, which may have long-term impacts on organism fitness and survival. Fundamentally, the collection of networks connecting hierarchical levels will improve our understanding of the Rules of Life.

**Why now?** Diverse, open source “big-data”, such as omics data (genomics, proteomics, metabolomics), ecological data (soil and climatic), and biodiversity inventories, are becoming increasingly available. Such large-scale information permits complex modeling of biological system processes at multiple scales. New methods are also available to integrate big data at the micro-level (e.g., to build gene regulatory networks of biological pathways [4]) and at the macro-level (e.g., ecological niche modeling to predict shifts in species distribution range when responding to climatic changes). However, the connection of processes at different levels of analysis remains largely unknown because of the many challenges outlined below.

A better understanding of how processes at one scale affect mechanisms at another scale requires diverse data and data integration across different biodiversity scales and from diverse organismal/ecological systems. New omics tools and long-term ecological monitoring systems allow for data collection that fills in gaps in knowledge for a more complete picture of processes at different hierarchical levels in diverse systems. The new data will provide the basis for understanding how process networks at one level affect those in another. New tools for

modeling gene regulation networks, protein networks, iterative in-silico modeling frameworks including Artificial Intelligence, and mathematical modeling tools for extracting biological information/knowledge from molecular or higher hierarchical level networks continue to emerge for tracking multi-level interactions. Multi-scale modeling is now an active area of applied mathematics with potential approaches that have already been demonstrated to be directly applicable to hierarchical aspects of biological systems (see MultiScale Modeling Consortium supported by NIH [5]). New technologies that are emerging for real-time imaging at micro and macro scales including estimates of functional connectivity, improved remote sensing with improved spectra-spatial-temporal resolution, and state-of-the art microscopy. In addition, subtractive modeling approaches and computational tools are available to develop novel integration across scales [6]. Across-level modeling is particularly important to determine the deep effects of environmental change on biological systems. This issue is of urgent importance at the society level. Understanding how processes communicate and affect one another across scales allows prediction of organismal and population responses to climate change.

**What are the state-of-the-art technologies and applications?** Based on the current state of technology and the focus on networks across levels, there is great potential for new technology to be integrated and developed beyond the current resolution. Emerging technologies allow for visualization of complex processes across levels for real-time systemic analyses including design sensors amenable to multiscale measurements.

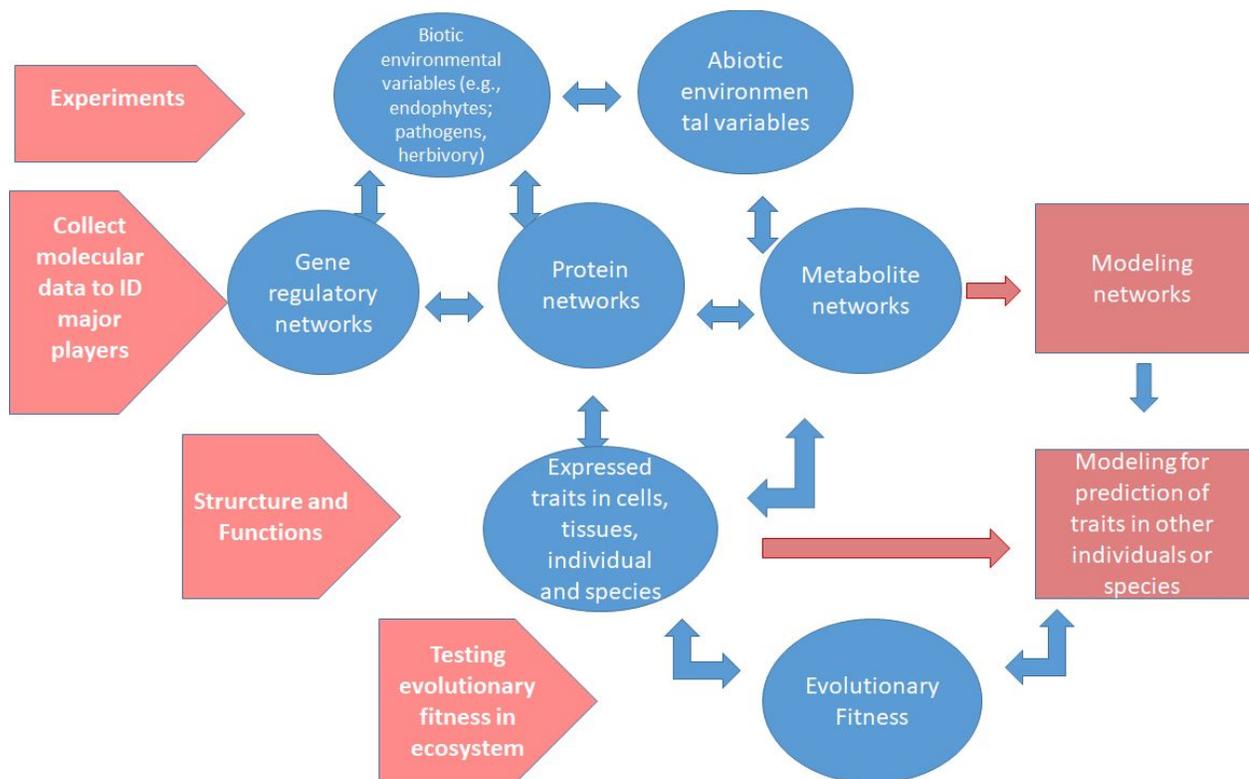


Fig. 1. An example of integrating information from different scales to understand complex interactions at different levels of biological organization. This can be done for different species

on a phylogenetic framework to understand the evolutionary trends of these networks and interactions for prediction of influences of biotic and abiotic factors on the future evolutionary fates of living organisms.

**Key barriers and challenges we must overcome.** Barriers and challenges to the proposed advances exist at multiple biological levels. These challenges present key areas for focused inquiry and funding support. Specific challenges within levels of biological organization include identifying key functional elements within and across each network/level. This requires: (1) efficient measures of functional elements within level to provide ample data (genes, proteins, cellular processes, organ and organismal-level processes, ecosystem processes, etc.). (2) network analyses to characterize how functional elements interact within and among levels. These will allow identification of the key/hub elements within each system at each level of analysis. This process can be facilitated through the use of -omic technologies and network analysis methods that are already in use at some levels/scales. Improving the design of databases and information depositories to make them more usable by researchers in other disciplines through explicit metadata and usable extraction tools. Additional development of AI tools to search databases and extract relevant data to address a particular research problem is also needed. Further, identifying and extracting common metrics within each level of organization would allow us, and AI technology, to more easily identify and characterize connections across levels. Information within each level of analysis provides the basic building blocks to test cascading pathways among levels (from ecosystem to organismal to cellular and molecular processes). A challenge to modeling communication/interaction across levels of networks will be the identification and quantification of key pathways, feedback mechanisms, and measurement at appropriate time scales. However, identification of some core pathways across levels will allow us to test the benefits of such cross-level communication/interactions in predicting complex multi-level organismal and ecosystem responses to environmental challenges. Methods to facilitate this cross-level modeling include a first focus on model systems that are well-characterized to best determine potential benefits of this complex cross-level modeling (for example using hierarchical Bayesian methods). One potential benefit is that we may be able to identify universal principles that exist within and across levels of analysis.

**Broader impacts.** Knowledge of the nature and types of feedback interactions that occur across biological scales, would greatly enhance our ability to demonstrate mechanisms. For example, our ability to understand phenomena observed at one level of biological organization may only be possible by incorporating knowledge of processes that occur at other levels of organization that directly influence the phenomenon we observe. Knowledge of the network structures connecting different levels of organization would also greatly enhance our ability to tackle really complex systems, e.g. predicting the impacts of climate change across biological levels of organization, where innumerable feed-back loops compound our ability to draw conclusions that could inform policy-making, governance, and emergency preparedness. Indeed, such knowledge would provide a better understanding of the depth of environmental effects on organisms/populations in general. Filling this gap in our knowledge would also enable

us to design solutions to remediate global problems while minimizing the risk of unanticipated adverse effects resulting from these remediation efforts. These efforts would include reversing environmental degradation, enhancing the efficiency of food production to feed a growing population, improving global health and addressing health disparities. We can also apply this knowledge to address additional practical applications including identifying susceptibility to disease and injury, and address problems associated with aging. We could also apply this knowledge to alter the way that we treat medical conditions. For example, when systems such as muscle are perturbed, at what level should we restore this system? In this case the most effective treatment may be to target a deeper determinant level (e.g. proteins) than treating the manifestation itself (i.e. contraction).

**Reintegration of Biology and Contributions from across STEM.** The goal is to inform the advances needed to progress to a stage in biological research where we are capable of generating predictive network models of the relationships existing across different levels of biological organization. This will enable us to explore how these relationships vary (or remain invariant) across systems built with different levels of complexity. These goals will require substantial (re)integration of knowledge from across disparate STEM fields, not limited to biology.

Necessary contributions will include participants that collect comprehensive basic datasets from suitable candidate systems (i. relatively low-complexity systems, ii. model-organism systems where data exist at most levels, iii. high-complexity systems, or challenge-pinnacles). To explore relatively simple interactions, data can be subjected to *in-silico* modeling approaches including finite element analysis (engineering stresses), biomechanics (OpenSIM), ecologists (MaxEnt), physics (Simulink), geneticists (ImuSys), etc. Computational scientists will then need to generate network analysis approaches, capable of dynamically relating data from determinant-level “sheets” (formed by the above-mentioned modeling approaches) to each-other; this could be helpful for initially establishing system interconnections across levels. Using artificial intelligence approaches, it may then be possible to establish general patterns of feed-forward/feed-back in response to system state-changes that either result through predicted processes (maturation, aging) or episodic state-changes (injury, climate change). *Insert final statement here once distilled down.*

#### **Intended audience of the paper.**

Advanced undergraduates, budding graduates, students of 21st Century biology.

#### **Glossary**

**Levels of biological organization** (or determinant levels, organizational levels, biological hierarchy, scales (sounds to be a reserved word, large-scale).

**Levels** (or sheets, layers, planes, scales)

**Signalling** (reserved for molecular information flow)

**Pathways** (information flow within and between levels)

**Interactions** (information flow within levels)

**Entities** (as opposed to components, players)

**Processes** (interactions)

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