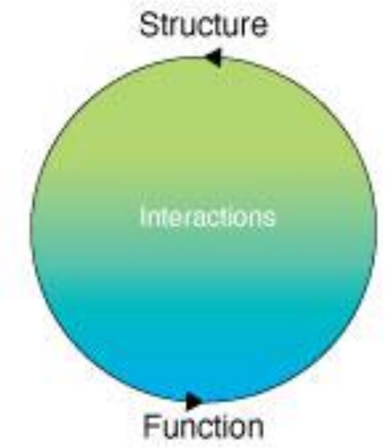
Title: How do interactions drive dynamics of structure and function?



Authors:
Hernan Garcia-Ruiz. University of Nebraska-Lincoln.
Brett Aiello. Georgia Tech / Florida Museum of Natural History
Christine McBeth, Fraunhofer USA CMI / Boston University
Emina A. Stojković, Northeastern Illinois University, Chicago, IL
Nir Yakoby, Rutgers University, Camden NJ

Defining terminologies:

Interactions are broadly describe, indirect or indirect, transcending from micro to macro scales starting atomic, antigen-antibody, host-pathogen, organism-environment, environment-environment. This broad definition of interactions is important to reintegrate across the subdisciplines in biology.

Dynamics are used as a term to define the constant change in our ever evolving world across femtoseconds to billions of years.

Structure and function are directly related and influencing one another through a constant, reversible feedback loop. Structure determines function, and function informs structure on subatomic to the organismal level and beyond.

What's the big question? What's the exciting science?

At all scales of biology there are interactions between structure and function, from nucleic acids, proteins, cells, organisms, ecosystems, the entire planet earth involving time. Functionality may drive the selection of structures that determine phenotypes with competitive advantages. In a feed-back-loop, structures are determinants of function. The dynamics of the interactions are influenced, possibly determined by environmental factors imposing selection pressure on functionality. A fundamental component of the dynamics is the sources of variation in structure and in function. A clear determination of cause and effect would help understand the dynamics between structure and function.

Theoretically, an entity in equilibrium with the environment will be perpetuated in the absence of disturbance. In the absence of a source of variation, selection forces requiring new functions will eliminate the entity. In an opposite direction, an entity capable of generating diversity is more likely to provide the function needed to adapt/overcome the change. Under these scenarios, new structures may ultimately code for new functions.

In an alternative approach, a single function might be supported by different structures. Changes in the environment may require new functions. Some structures may be more capable of evolving to meet the new requirements, and eventually be able to execute new functions.

To understand the dynamics between structures and function, fundamental questions include how might we identify and separate cause and effect? What are the sources of variation in structure and in function? What are the forces that drive selection of structure, selection of function? Are there factors that affect both structure and function?

Approaching biological questions from multiple perspectives and disciplines provides a more holistic and robust understanding of the processes contributing to the dynamics of biological organization and how changes in the structure of a system influence functional output. Interactions between biological entities can and do occur across levels of biological organization, and the structure/function relationship at one level of organization often impacts those at other levels. A reintegration of approaches from across disciplines will unlock untapped potential to answer fundamental questions in biology. Here we outline an example of one question that crosses scale (from the molecular scale to an ecological arms-race) to be answered that requires a reintegration of biology:

We argue that interactions that begin at the molecular level can ultimately impact species interactions at the eco-system level, and that interactions at the ecological level are ultimately driving changes at the molecular level. In sum, reciprocal interactions along both directions of molecular to eco-system continuum drive the evolution of structural interactions and their functional output.

One particular example is an evolutionary arms race between a predator and prey. Animals have multiple predators that need to be evaded in order to increase its chances of survival, and ultimately, its fitness. Animal movement arises through the interaction of multiple integrated physiological systems with the physical environment. The ability of an animal to evade a predator could depend on its neuromechanical output – its maneuverability or locomotor speed, for example. Let's now track how selection for increasing locomotor speed at the ecological level can impact changes at the molecular level. A given speed can be achieved by increasing the frequency of the locomotor cycle of an animal or the force produced per locomotor cycle, among other variables. Animal movement is often driven by a suite of muscles. A selective pressure to increase muscle force output could be manifested through selection to drive the locomotor cycle faster or over a greater amplitude. Muscle itself is a composite structure composed of multiple cells. The subcellular level of muscle can be further broken down into repeating sarcomeres that contain the thick and thin filaments which are composed of proteins (myosin and actin, for example). The arrangement of the thick and thin filaments and the particular isoforms of proteins are under strong selective pressures and have variation across different tissues of a single species (heart versus skeletal muscle) as well as differences in a single tissue across species. Changes in the protein isoforms or the arrangement of thin and thick filaments at the sarcomere level translate to differences at the whole-muscle level. Tracking this change back towards the ecological arms-race previously outlined, these whole-muscle changes can impact locomotor output, which impacts force and/or frequency output, which impacts the ability of a prey to evade a predator, which then puts further selective pressure on the predator to evolve similar or different changes.

What's the potential impact?

The dynamics driving structure-function interactions cross all scales of biological organization. Understanding these dynamics has potential to develop a novel framework to inform biology, generate predictive models. These models will feedback into tested how well do they recapitulate the actual structure.

Why now?

We are living in an era of technological revolution that generates large amounts of quantitative data at multiple scales, including the molecular, cellular, tissue, organismal, and ecological levels. In addition, model systems are highly diverse even within each level. Looking at publications resulting from the use of high throughput platforms, in particular at the molecular levels, only small portions of the data are being used, and consequently, much of the data are left out.

Many disciplines in biological sciences use similar tools, however, the communication among scientists and data sharing between scales is limited. Since the building blocks of organisms are the same, using inclusive data may enable to identify common primitive patterns of networks at each scale. These patterns may serve as "biological universal principles" across domains and scales, and may provide a direction for the missing links at each structure. At this time, we are able to develop platforms to synthesize heterogeneous data that can direct the identification of common patterns along and across scales. The platform will enable to identify commonalities as well as uniqueness structures in scales.

What are the state-of-the-art technologies and applications

With current genomic technologies, it is possible to determine the microbial composition in the soil, water, plant roots or leaves, the species composition of any ecosystem and their fluctuations over time.

One of the challenges at the molecular, cellular and tissue scales is the low resolution of in vivo interactions. Many interactions are deduced indirectly by outputs and not directly driven by the actual processes. "Nano-cameras" can provide real time picture of the member of the network/structure that produce a function. These functions can move to the next scale.

Elaborate the key barriers and challenges that will need to be overcome.

Communication of questions and results across disciplines.

Dissemination of information to the broader community must be incentivized. Publication or public availability of data is not sufficient. The disparate nature of the fragmented data landscape precludes efficient information transfer across scales, systems, and disciplines. As biology is re-unified, there must be international standards developed in parallel to provide the language and tools to enable this re-unification. Biology superdefinitions that rise above the disparate definitions of structure and function must also be integrated with bioinformatics conventions to accelerate computational modeling approaches. Biology standards would drive visualizations that yield novel insights generating new avenues of research feeding back into the specialist communities.

Technological barriers

Biology suffers from endpoint processing. Cells are lysed, tissues are fixed, animals are dissected. The tremendous efforts in real-time monitoring of life itself—live cell imaging, population migration tracking—demonstrate the power of this approach. Significant investment in real-time monitoring of life at all scales would drive new discoveries and allow for more complex interactions to be developed. As an example, in cell biology, much of the work has been conducted in flat two-dimensional cultures. The low cost of manufacturing microtiter plates and surrounding instrumentation led to this explosion of research. However, cell behavior in their natural habitat—the tissue—is radically different. Tissue engineering approaches involving cells in 3D cultures is still severely hampered by endpoint processing. The manufacturing costs of building 3D structures and microtissues is too high to sufficiently explore the interplay of all the factors (biological—growth factors, media choices, mechanical—surface roughness, material stiffness, and so forth) across multiple time points. That is, researchers guess when to collect time points. The development of real-time monitoring systems that are highly responsive to manufacturing costs would drive the next big bang of biological discovery.

Lack of these tools is a pressing bottleneck that prohibits reintegration of biology. These real-time reporters generating data in the complex environments, rather than reductionist, isolated, fragmented samples, would allow teams to capture the interactions of biology across scales. We could perturb a molecule and monitor the molecular interactions, cellular interactions, and even up to host-pathogen and predator-prey relationships. It is the vision of one input-multiple outputs simultaneously reflected back in real-time to visualize these connections.

What might be broader impact?

Fundamental understanding of the dynamics driving interactions between structure and function would allow multiple applications, such as designing novel drugs, biomaterials, resilient crops, biodegradable materials, manipulation of microbial communities for bioremediation, predict phenotypes from genomic sequences, design phenotypes by manipulating genomes, communities, the environment or their interactions, predict organismal adaptations to changing environments, predict the effect of genetic mutations or perturbations on species diversity, identify novel biological entities and properties.

This is incredibly interdisciplinary topic with a potential to generate new and exciting science from micro to macroscales to entire ecosystems and beyond. Starting with unifying general theory and models that span subdisciplines of STEM, defining the interactions that drive the dynamics of structure and function as we envision originating on sub-atomic level and spanning beyond our planet. Within the constantly evolving adaptations to environmental stressors, we have the ability to predict how our world may look in the near and far future.

As such the community involved in the research spanning this revolutionary topic, has to develop and follow strict ethical guidelines on global level to avoid dangers of unintentional and possibly intentional dangers of genetic, chemical, environmental modifications spanning across the scales of biological entities as we know them. Students of all levels - early school to post-graduate education will be involved in state-of-the-art science spanning various subdisciplines. Interdisciplinary training and development of novel computational and mathematical tools will result in a community of young scientists excelling in skills and methodologies versatile on all levels of STEM disciplines. The education and training component of these actions will generate a new workforce of interdisciplinary, well-rounded, and creative young scientists that are able to contribute at multiple levels to society. Funding agencies have the responsibility to facilitate training grants to integrate them into existing and new work avenues, including academia, federal, state, industry, and start-up/incubators. Contingent work is not a solution. This step has to be integrated as we move forward with generating new training disciplines.

How does it reintegrate biology?

We also outline the connections between a subset of disciplines and how reintegrating biology can contribute to a few different fields in STEM:

Evolution: The link between form and function provides an exceptional opportunity to view evolutionary patterns and processes. A strong selective pressure driving the evolution of a biological entity will influence both the entities it directly interacts with to produce a given function, but also systems across scales of biological organization.

Paleontology: An understanding of how interactions between the integrated systems / structures of organisms relate to function will allow us to better interpret the functional capabilities of extinct organisms as well as how those organisms could have assembled in communities and their role in the ecosystem.

Neuroscience: Dynamic interactions between neurons, and changes in the various structures (e.g. neurons) involved in the process can change the outcome of the process / function. This is another exciting place where we can find examples ranging from the molecular to ecosystem levels. Example: selection on the ion channels of a neuron (or population of neurons) impact neural physiology. In sensory neurons, physiology is often evolutionarily tuned to maximally detect the relevant stimuli in the environment of a specific species.

What disciplines might be needed?

Many disciplines are needed to answer this big question and address the exciting science. Primarily STEM, including researchers and educators from each of the subdisciplines and all levels of education, undergraduate, graduate and post-graduate as well as early K-12 teachers.

Intended audience of the paper.

Colleagues in STEM - biologists, engineers, chemists, physicists, mathematicians, earth scientists, computer scientists, public-health scientists, psychologists, anthropologists.