What functions are common across scales and do common structures enable those functions?

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Introduction

Many functions (such as transport of a substance and sensing the environment) are needed at biological scales from a submicroscopic protein complex to an entire ecosystem. Similar functions are sometimes performed by similar structures, but in other cases similar functions are performed by different structures. A comparison of functions and the structures that perform them across scales would provide several types of valuable information.

Here we focus first on looking for similarities in functions across biological scales, then explore the structures underlying those functions to identify similarities and differences. This perspective differs from the more traditional building block approach in which the structure is examined to predict or infer function. One advantage of this "reverse" approach is that it encourages biologists across the scales to work together to improve our understanding of these functions.

Connecting structure to function is not always straightforward, but for many functions we already have information about the connection between structure and function at one scale, and a comparison across scales may help in developing testable models of how a function works at other scales. Comparisons could aid in identifying the key structural elements within a complex structure and help in elucidating the simplest model. It could also suggest that a previously unobserved structure and/or function might also exist at other scales and even where to look for it. These comparisons can also be expanded to include considerations of how functions of different structures might vary over time and how the time scales can vary.

Identification of commonalities will, of course, lead to identification of differences. Understanding differences would improve our ability to predict the function of a structure. These differences also provide information about the different ways to perform a function, for example, different structures that could transport an entity from one place to another. In some cases, the differences in structure and function seen across scales could be due to the dominant physical principles that differ across scales and would provide information about how the forces can be used or addressed.

This approach can be applied widely for many types of structures and functions and across many scales because we are defining "function" as what a biological unit does. This can include activities as diverse as a receptor binding a small molecule or the productivity of an ecosystem. We define "structure" as the shape and composition of a biological unit. A "shape" is a description of the 3-dimensional morphology. Different types of structures exist in biology, and the different types of structures can have analogies across scales (for example, the three-dimensional shape of a protein and the three-dimensional shape of a limb). "Composition" is the number and type of building blocks from the biological level smaller than the current one, for example, cells are composed of cytosol, proteins, DNA, etc., and populations are composed of individuals. Our definition of structure can be expanded also to include other types of compositions and arrangements, for example, a group of different proteins forming a biochemical pathway or a group of different organisms forming a population. The scales we are considering include, but are not limited to a molecule (for example, proteins), organelle, cell, tissue, organ, organism, population, community, and ecosystem. Examples of functions that could be considered across scales would include energy transformation, matter transformation, transport, movement, sense and response, and reproduction. More specific questions might include:

a. Can we gain novel insights into movement by comparing how motor proteins interact with the cytoskeleton to move organelles to how the muscular and skeletal systems interact to allow an antelope to move across the savannah?
b. Or into transport by comparing how molecules (e.g., sugars, amino acids) move across a membrane (via channels/pores/transporters) to how food moves through the gut of an organism (through a similarly shaped tube)?
c. Or into assembly by comparing how cells assemble cell walls and how bees assemble hives or beavers build dams?
d. Or into communication by comparing how cells communicate through hormones with how birds communicate in a flock or fish in a school?
e. Or into transport through ecosystems or organisms by rivers with tributaries or the circulatory system with arteries and capillaries?

Potential Impact

Comparing structures across scales will allow us to identify gaps in knowledge at specific scales and inspire new questions about how structures work. Identifying universal principles from similarities in structures across scales will improve our ability to predict function from structure and therefore develop predictive models about how structures relate to function and how these relationships vary across scales.

Another advantage of having a better understanding of the universal principles that relate function to structure is an improved ability to create structures to perform a specific function. The potential for bioinspired design spans scales, from inspiration for advances in nanotechnology at the molecular scale to harnessing biological designs to create more efficient human-used structures, from tools to cities. Moreover, explicitly considering scales allows for prediction of the spatial and temporal bounds at which biological processes could be adapted in engineering design. The potential for multiple structural solutions for a given function that may or may not depend on scale will provide insight into evolutionary processes as well as broaden the potential for bioinspired design. Rare solutions to functional problems could lead to new avenues of research to understand the limitations.

This perspective on biological functions has the potential to transform undergraduate education by focusing biology curricula around broader concepts based on functions rather than specialized scale-specific disciplines (as proposed for biology education in the document *Vision and Change).* By presenting science as a puzzle with problems (functions) and solutions (structures), students will improve their ability to draw connections and move away from rote memorization of facts. Problem-solving will motivate students and encourage long-term engagement as well as better prepare them for graduate school or the workforce. Moreover, by integrating physics and chemistry into the curriculum as governing principles and introducing tools from engineering and computer science, students will have interdisciplinary training.

Why now?

This approach is timely as we have accumulated a large body of knowledge relating structure to function, creating a solid foundation on which to build a broader understanding of fundamental principles of biology that span scales. Synthesis of this information in a broad functional perspective framework will help identify gaps in our knowledge at specific scales.

Recent advances in technology have enabled us to better link function and structure within subdisciplines of biology and even to explore problems that integrate multiple scales. Technological advances allow for determining structures of larger, more complex proteins, and we are gaining better understanding of the structures of larger combinations of proteins through Cryo-EM and tomography. At the organismal scale, micro-CT scanning combined with finite element modeling allows for hypothesis testing of how complex structures such as skulls work, e.g., to resist damage. Drones and high-resolution satellite imagery allow for mapping ecosystem structures on spatial and temporal scales that would previously have been cost and labor prohibitive. This opens up exciting possibilities to link changes in ecosystem structures to functions and to link processes on large scales to organismal processes that can be more easily measured. On the micro-scale, technological advances in labelling allows for in situ observations of RNA and proteins within an organism, opening up exciting possibilities for linking molecular scale structures and functions to organismal parameters.

Finally, technological advances as well as a growing interest within the engineering community in bioinspired design creates a demand for a better understanding of how function and structure relate in biological systems. Advances in rapid prototyping methods at larger scale such as 3-D printing, laser cutters, CNC routers, and milling machines allow for affordable and rapid development and testing of new engineering designs. Nanotechnology is poised to take advantage of inspired design from molecular biology.

Key barriers and challenges

One barrier to making progress toward addressing this issue is the difficulty of disseminating the findings in one system to a broader audience so that the members of the broader audience can make the connections appropriate in their field(s) and at their scales(s). One possible way to address this difficulty in disseminating our findings would be to develop databases (or modify existing ones) that store information in such a way that it can be accessible by biologists studying at any scale (that is, would be universally accessible and usable by any biologist), requiring relatively little specific training. For example, could we design a database that houses information on protein functions and structures in such a way that the information is readily accessible to organismal biologists or ecologists?

A second barrier in making progress toward addressing this issue is the difficulty of identifying such commonalities, given that training in the biological sciences tends to focus on one scale. (We are typically not trained to think across the different scales.) One possible way to address the difficulty of any one person or group identifying commonalities across scales would be to hold cross-disciplinary workshops/symposia that bring together biologists with expertise at different levels to discuss and identify the possible functional connections across scales. In addition, encouraging graduate students to incorporate the question of how their findings might apply across scales (e.g., as a component of their graduate school program) might lead to the development of a generation of biologists for whom such thinking is second nature.

Broader Impacts

In addition to its impact on the education of undergraduates pursuing majors in the biological sciences (described above), presenting biology as a set of challenges that need to be addressed instead of a collection of facts might inspire students not pursuing degrees in the biological sciences to develop a more integrated understanding of biological principles, a clearer idea of the process of biological inquiry, and a better appreciation for its potential applications. Given the significant impact biological discoveries and applications have (and will continue to have) across society (e.g., in medicine and in agriculture), a more scientifically literate population will be able to make more informed and more rational decisions about biologically related issues.

Consideration of this question also broadens our perspective as biologists and researchers, as it shifts the focus to a consideration of functions and structures that span multiple scales and away from a focus on scale-limited functions and structures. Such a focus will require the cooperation and collaboration of several people whose collective expertise and focus spans several scales and allow for a more holistic approach to fundamental biological questions.

It also provides a mechanism for communication among the different subdisciplines of biology by encouraging those members of the community whose interests focus on the same function (broadly-defined) to work together to identify how that function (and the associated structures) plays out at the different scales. Answering this question will benefit from collaborations and communication among biologists across scales, biophysicists, biochemists, biomechanics, computational biology/bioinformatics, system biologists, and possibly engineers (mechanical, chemical, electrical engineering).

Bio-inspired designs will not only impact the field of science (as outlined above) but will also have broader societal applications. Our findings might, for example, provide information that would lead to more effective city planning, such as how to address the challenge of moving materials into and out of a city. This transport currently utilizes cars, trucks, trains, planes, and ships, but what is the optimal ratio among these different levels? Given that cellular transport involves players of different sizes and different mechanisms, can we apply our understanding of transport in cells to this larger question? Where is the energy coming from that runs this system and how can that energy be used more efficiently? Additionally, we might be able to apply what we learn from thinking about the commonalities of function across scale to design more efficient solar cells, more efficient drug delivery systems, and more efficient water treatment methods. These findings might also provide more information for the development of synthetic biology, including modifying biological entities for societal, environmental, and ecological benefit.