

From Flatland to Jupiter: Searching for Rules of Interaction Across Biological Scales

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Summary:

In this perspective, we ask the question, are there general rules for interactions across biological systems and evolutionary time? We then speculate how answering this question would advance the scientific enterprise.

Importance

In Edwin A. Abbott's novel Flatland, a line questions its two dimensional world to abstract about hierarchical structures. In a similar sense, scientists are at a tipping point in which the questions we can examine have the potential to dramatically expand our field of knowledge, enabling us to decipher governing principles, referred to as "rules," that guide biological processes. How would the scientific enterprise change if we knew the general rules for interactions across biological systems and evolutionary time? Could we decipher the mechanisms of biological communication as a form of interaction? And, importantly, are there features that can be applied across spatial, temporal and hierarchical scales? Answering these questions would allow us to interpret, predict, and modulate biology for diverse objectives. Here we examine the feasibility of addressing these questions, highlighting why now is an opportune time, and identifying key barriers and ideas for how to overcome them in a manner that gives rise to new science that enables transformative breakthroughs.

Why Now

Recent advances in biology have been staggering - whole genomes can now be sequenced in a single day for the price of a small laptop computer and then modified to the precision of a single base pair; the entire molecular contents of the human cell can be catalogued and localized to nanometer precision; the effects of climate change on whole ecological communities can be mapped through space and time; and our ancestry can be traced to the earliest life forms about 4 billion years ago. With the emergence of new technological capabilities, and thus experimental data, come the challenge and opportunity to make sense of it all. In 2017, the NSF launched its initiative on "Understanding the Rules of Life," aiming to elucidate the sets of rules that predict an organism's observable characteristics, or phenotype. In parallel, a community shift is emerging among scientists to work collaboratively and integrate data across fields. It is now time to take stock of the challenges that present particular barriers in this effort and expand its scope to identify those principles of biological interaction that apply across the spatial, temporal and hierarchical scales of biology.

To this end, we need to examine biological processes at several levels from molecular to organismal to ecological and systems networks (e.g. RNAi, neuron, macromolecular structures,

predator/prey interactions). Additionally, taking full advantage of the recent advances in measurement and analysis technologies will require training of the next generation of interdisciplinary scientists in a way that equips them to tackle true “Jupiter-shot” questions, integrating and synthesizing approaches from many disciplines to reveal universal truths that will allow us to shape our future.

Key barriers and ideas for breakthroughs

In order to uncover potential invariant interaction principles, we envision taking an agent-based modeling approach, applied across spatial, temporal and hierarchical scales. First, we need to identify relevant interacting agents. The agents can represent a range of entities from single molecules and subcellular organelles through tissues and organisms, to entire ecosystems over time. To achieve this, we will benefit from integrating existing and developing collections of data from a variety of sources (i.e., GenBank, PDB, BOLD, PLANTS, GBIF, MODs, etc), as well as by expanding the cadre of model systems to discover potentially novel agents. Next, we need to determine the possible rules of interactions. For example, how can we capture all possible media of communication, including both matter and energy? How can we determine at which scales the rules apply? Moreover, how might we identify a rule that is independent of scale (temporal/spatial/hierarchical)? Additionally, are the rules context-dependent, deterministic vs chaotic, or constrained in a manner that limits the possibilities for future interactions? To clarify these concepts we may need to employ novel measurement approaches, such as real-time monitoring of unperturbed dynamic systems ranging from single molecules to organismal networks that allow us to capture interactions between entities within and across scales. Finally, we need to define relevant minimal systems, sufficient to capture complex, emergent behaviors, while being elementary enough to translate across multiple scales. The challenge here will be to determine key features of the system and how they need to evolve. For example, to what extent could models developed within a spatial scale be applied to problems within temporal scale? How does the directionality of time limit our ability to deduce future outcomes from sampling the space of agents and interactions in a given moment? Developing new theoretical and modeling frameworks and testing them in these relevant minimal systems will ultimately facilitate our ability to predict outcomes of interactions at all scales.

New Science

Finding the interaction rules across biological scales will allow us to identify the drivers of biodiversity, predict adaptive evolutionary processes and design genes for robustness and resilience. Imagine if it was possible to look at a sequence of DNA, RNA or protein and be able to identify its molecular function and predict the temporal, spatial and hierarchical interactions it will have within a cellular systems network. Now imagine how those interactions will impact organismal behavior and how that behavior will influence evolutionary processes from the neofunctionalization of genes, to the birth of a new species, to the inhibition of enzymes, to the extinction of taxa. The analyses of these rules of interaction combined with newly available technology will decipher the code of communication, where communication is defined as the transfer of information between agents. For example, we will be able to explain why there are so many different biological species, and how diverse organisms assemble, live in, and share the same environment. If we understand communication among different biological entities and their

common environment through millions of years, we will be able to predict how they will adapt to change. And more importantly, we will learn how to cope with unexpected changes that have catastrophic consequences. For example, we would be able to intervene when a species is in danger of extinction. Additionally, the knowledge of these rules of interaction across biological species and evolution will provide a roadmap for synthetic life from single cells to organoids to complex organisms.

Scientific and Broader Impacts

Identifying the principles that govern interactions across biological systems and evolutionary time will explain the connections that enable and facilitate function. In determining principles that can be applied across spatial, temporal and hierarchical scales we will begin to illuminate the evolutionary arc from the origin of life to the present. One exciting aspect about such horizon spanning initiatives is that it forces a reexamination of existing scientific approaches. To this end, pursuing an initiative that identifies interactions across biological systems and evolutionary time will enable paradigm changes in STEM education that facilitate transdisciplinary training of students and restructuring of academic departments. Finally, tackling this problem will provide tools to mitigate societal challenges related to natural disasters and global health.

(Synthesis notes: We envision that groups 12, 21, and our group could be published or linked together to represent Moon, Mars, and Jupiter shot challenges, respectively.)
