Working Title: Integrating biology to understand communication across scales

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Summary:

Communication is a fundamental property of life at all scales from organelles to ecosystems. During communication, one actor (the sender) uses a specially evolved trait to modify the behavior of another actor (the receiver). Thus far, we know little about the similarities and differences in communication across scales. For example, do similar properties mediate communication between molecules and communication between organisms? Understanding commonalities between communication systems across scales could: provide insights into coevolutionary processes, allow modeling of communication patterns in response to environmental changes, have application in bio-inspired design, and lead to better predictive models of disease spread. Reintegrating biology will require broad-scale changes in training and infrastructure, and we suggest new programs to facilitate this work.

The Big Question:

What are the commonalities among communication systems across scales? Do communication systems respond similarly to environmental change?

Communication is a fundamental property of life at all scales. There are no biological entities than don't communicate. Functional biological systems depend on effective information (chemical, auditory, visual) transfer within and across scales. Communication, broadly defined, is a fundamental coevolutionary process. A key question in biology is how traits evolve when selection in one actor depends on the phenotype of another actor (e.g. mutualism, predator-prey relationships, cooperation, communication, quorum sensing).

Definition of communication:

Communication is when a sender uses a specially evolved trait to modify the behavior of a receiver. The sender is the individual producing the signal, and the receiver is the individual responding to the signals. Traditionally, senders and receivers are individuals. For example, a male cricket singing to attract a mate is a classic example of communication. However, for the purposes of this paper, senders and receivers can occur at any scale (e.g. organelles, cells, organs, organisms, and populations). For example, some freshwater mussels attract fish hosts with a visual lure to increase the successful attachment of their glochidial larvae. Similarly, tissue-level stress signals can induce transcription within the nuclei of single cells. At higher levels of organization, species may secrete substances that attract other species that they use as food. A good example of this is benthic infauna that line their burrows with mucus which is a substrate for their microbial food source. Another example would be parasites altering the behavior of their host to benefit the parasite's proliferation. Communication can occur in any sensory modality, including visual, olfactory, acoustic, electromagnetic, or chemical.

By definition, communication must provide a fitness benefit to the signaler. As a result, males singing to attract potential mates is communication. However, traits that do not benefit signalers are not considered communication, even if those traits provide information to receivers. For example, mosquitoes use CO2 to find hosts. CO2 production by hosts is not communication, though. It is merely a byproduct of physiological processes that mosquitoes use to find hosts. Similarly, carbon or nitrogen flux from decaying salmon causing changes in the nearby stream and forest ecosystem is not communication because the salmon do not benefit through the chemical transfer.Information transfer that occurs between generations is also not communication, but is similar in many ways.

Thinking about the selective benefits of communication is important because the selective benefits mean that communication involves a co-evolutionary process between senders and receivers. While co-evolution is most often used to refer to reciprocal evolutionary change between two different species, we use this term more broadly to refer to the ways selection might shape two interacting entities at any scale of biological organization. Therefore, co-evolution can occur within a single species or entity. As a result, sender and receiver phenotypes are strongly shaped by the benefits and costs of effective communication. An example of communication across scales is provided by hormones that are produced within cells, have implications for organism physiology and behavior, communication between organisms, and potentially across species (e.g., plants producing ethylene gas causing flowers and fruits to ripen and increase animal visitation).

Exciting questions that could be addressed:

1. Can modes of communication at one scale inform our understanding of communication at another scale (cells to organisms to populations)? Are these patterns consistent across diverse systems?
2. What factors can we use to predict the similarity of communication across scales?
3. How can communication at one level of biological organization impact communication at other levels? (this is about feedbacks across levels)
4. How do novel types of communication originate among actors when it was not present before (e.g., evolutionary history, plasticity)?

5. How do modes of communication across scales respond to environmental change including novel environments? For example, an endocrine disruptor modifying communication between endocrine and target cells.
6. How might we predict and exploit communication systems?

What's the potential impact?

- We could provide insights into co-evolutionary processes within and outside of cells, organisms, populations, or ecosystems.
- We would be able to model or predict communication patterns in response to natural and/or human caused environmental changes
- We would be able to identify more efficient means of signaling in biological systems that could be applied in artificial situations (bio-inspired designs)
- We could develop better predictive models to explore how communication systems change with perturbation (e.g., unintended receivers that intercept communication) or altered cell signaling pathways (e.g., cancer and metastasis)
- As new types of interactions are detected among actors, this may provide new insights into the boundaries and definitions that we apply to biological systems

Why now?

1. Communication is a fundamental rule of life. Thus, to understand what it means to be alive requires understanding the rules that govern communication. Technological innovation means that we can measure communication at scales that weren't previously possible. As a result, we have an opportunity to think about commonalities across diverse scales.
2. Anthropogenic effects on the environment present new challenges for biological systems at all levels. In turn, these provide new opportunities to explore the evolution of communication.

What are the state-of-the-art technologies that are currently available?

New approaches are available to provide insight at all levels of biological organization, making broad comparisons feasible:

- Chemical level: Ligand binding and chemical modification to change the properties of macromolecules. New chemical technologies allow us to identify these relationships in more in-depth ways.
- Cellular level and below: The rise of "-omics" has allowed for new approaches (e.g. single-cell genome sequencing, DNA methylome, transcriptome, metabolome, proteome) to understand signaling within and among cells. For example, the intracellular protein AMPK sensing high AMP:ATP ratios and signals changes to the mitochondria and nucleus to coordinate aerobic metabolism to bring the cell back into ATP homeostasis. Phenome data can be used to identify signaling chemicals unique to

particular cell types or those associated with disease. This might first be tackled in "simple" systems like organoids in cell culture or in slime molds.
- Tissue level: Organoids (self-organized three-dimensional tissue cultures that are derived from stem cells).
- Organismal level: Modern gene-editing technologies (CRISPR, TALEN) to precisely manipulate phenotypes; virtual reality to manipulate the environment
- Population level: Animal-borne and other modern technologies (e.g., laser imaging to detect chemosensory signaling (e.g., Koehl et al. 2001) to sample interactions between individuals; individual-based models
- Multispecies level: multi-species models allow us to identify potential communication within systems. Modeling sensory systems of organisms helps understand what traits could be signals to conspecifics vs. heterospecifics (e.g., visual acuity: Caves et al. 2018; Smee & Weissburg 2006). Biogeochemistry and radio-isotope analysis allows us to measure how chemical information and resources move through the environment.

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

- How can we distinguish noise from actual messages?
- How might we identify the effects of the same force across differing biological scales?
- How can we identify communication across diverse levels or systems such that these data are comparable/useful?
- Communication occurs in many modalities and has diverse effects on the pheotypes and genotypes of senders and receivers. What aspects of communication will be most fruitful to compare across scales?

How does this question reintegrate biology?

This question brings together multiple disciplines and spans multiple spatiotemporal scales and levels of biological organization to produce new insights into a fundamental biological principle.

What disciplines might be needed?

Ecology, molecular biology, chemistry, cell biology, information theory, neuroscience and psychology, quantitative/mechanistic modeling, structural biology, biophysics

Broader impacts

- Integrative training keeps doors open for people.
- Provides new opportunities for citizen science (documentation of interactions among organisms)

Mechanisms to improve integrative training

Re-imagined DDIG program: Opportunity for graduate students to visit a different lab (very distinct from their home lab). Comes with research funds.

- *Pros:* May open up new future areas for the student that could result in an increased possibility the postdoc is in a different area of study.
- *Cons:* Might slow down progress to a PhD. This could this be a distraction rather than a complementary investigation that adds to the PhD project and career arc of the student.

RCN-like program where the network is constructed of investigators who do not already collaborate or share collaborators (how many degrees of separation?)

- Pros: Answering these big re-interating biology questions does not necessarily mean generating new data, but instead might rely on putting data from different systems and scales together. So, funding new networks of scientists might be far more cost-effective than funding new, siloed science.
- Cons: Re-integrating is hard.

Train undergraduates broadly. Perhaps we need distribution requirements (where they aren't already, or expanded distribution requirements) in undergraduate curricula. Some specialist areas/majors (e.g., neuroscience majors, biochemistry & molecular biology majors, ecology & evolution majors) have 'curb appeal' to students, parents, administrators, but do not necessarily serve students well in the endeavor of reintegrating biology. We might also consider modeling this desired integration more intentionally in our teaching. For example, offer upper-level undergraduate courses or beginning graduate courses that are at the intersection of two co-instructors' expertise (e.g., ecoimmunology, behavioral endocrinology, plant development).

Broad undergraduate training also relies on faculty expertise and the ability of faculty to demonstrate integrated approaches for understanding fundamental biological phenomena. One challenge of undergraduate education is that students do not always see connections between related concepts that are presented in different courses. For example, the principles that mediate cell-cell communication have important parallels with communication between organisms. We need approaches that will encourage faculty to explicitly make these connections for students, (i.e. workshops that involve faculty from multiple disciplines or virtual mentoring networks that allow faculty to develop and test new ways to integrate concepts). While journal clubs and research seminars are likely standard in both undergraduate and graduate departments, department level efforts to promote reintegrated approaches to biology could include poster days.
At the department level, and perhaps guided by NSFs Vision and Change document, departments can develop a set of skill sets and knowledge criteria for their students that specifically encourage integrated thinking and that embed integrated approaches into the curriculum at every level.

Rotations are less common in ecology & evolutionary biology programs. Does this mechanism of training make more integrative biology possible? Are there ways in which rotations can be designed to introduce broad biological questions that require integrated approaches?

Biological level of organization	Example details	Citation (PMID)
Intra-cellular	Ligand binding and chemical modification to change the properties of macromolecules; intracellular mitochondrial signaling; Hormones	18922799; 31646532; 31797871
Cell to cell	Neuronal signaling pathways, Hormones; notch-mediated signaling	31718063, 31766724, 31794732
Organismal	Embryogenesis Hormones	
Between species	Volatiles emitted by plants and perceived by herbivores or other plants Hormones	Baldwin et al. 2002

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