Workshop Report

Biological Function in Space and Time: from Forces and Cues to Emerging Decision-making in Fates, States, and Shapes

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Overview

Biology is comprised of physical systems operating in space and time; like all matter, living systems are governed by causality and physical interactions. Understanding the way biology integrates information across spatial and temporal scales —from subcellular molecular signaling to cell-level responses, tissue-scale mechanics to organismal development, or animal behavior to collective decision-making— is an exciting open challenge in the field. The convergence of theoretical ideas from geometry, information theory, and control theory/reinforcement learning provides unifying concepts through which we can understand: (1) how to extract functionally relevant spatiotemporal descriptions from data; (2) how complex hierarchical structures are reproducibly formed and maintained; and (3) how robust decision-making emerges from spatiotemporal interactions. Especially with modern high-dimensional data, new mathematical frameworks are required to reproducibly describe how information is encoded and transferred across scales. Researchers from diverse biological subfields have developed formalisms and concepts adapted to their systems of interest; this meeting set out to find the principles those formalisms share.

The workshop brought together experimental biologists, biophysicists, and applied mathematicians from across North America, Europe, and India. Building on the shared scientific challenges outlined above, the workshop aimed to identify common challenges across disciplines, foster interdisciplinary collaboration, and develop a more unified understanding of biological functions across space and time. The program featured daily 45-minute participant talks, ample time for informal discussion and collaboration, and three volunteer-led discussion sessions focused on key topics. Regarding research approach, 53% of attendees identified as theorists, 17% as experimentalists, and 30% as researchers combining both approaches. Participants included faculty (50%), postdocs (27%), graduate students (20%), and other researchers (3%).

Scientific Themes

- *Oscillations as spatiotemporal event organizers:* Oscillatory mechanisms can robustly control spatiotemporal events in diverse biological systems. Oscillations can provide a useful clock that enables precise instigation of events (Kemal Keseroglu's talk on somitogenesis) or prevent habituation to a signal (Mark Greenwood's talk on hormonal regulation). When these oscillations are coupled with spatial feedback, they can generate waves that enable spatiotemporally ordered activation of events. Speakers Guillaume Salbreux, Danny Seara and Mark Greenwood highlighted how oscillatory mechanisms emerge in the growth of fish scales using ERK waves, energetics of cytoskeletal processes, and plant roots respectively.
- *Spatiotemporal Feedback:* Feedback can play a role in generating desired patterns, waves, or dynamical changes. We saw this in landscape evolution in cell-fate decisions, pattern formation across tissues and cells, and decision making. Mathematically understanding the

most robust strategies, mechanisms and commonalities in various feedback systems helps us understand the forces that give rise to stereotyped spatiotemporal patterns.

- *Cross-discipline methodological overlap:* Many of the same mathematical tools, such as information theory, dynamics on evolving landscapes, and control theory, were used to analyze disparate biological systems. This leads to an exciting opportunity, where lessons learned in one domain can be translated to a new context. Can tools developed to understand high-dimensional gene inputs relate to low-dimensional cell-fates? Can tools developed to understand low-dimensional decision making in high-dimensional environments uncover common theoretical foundations?

- *New data-driven and theoretical tools*: MathBio is experiencing rapid development of new theoretical frameworks to understand and analyze complex biological phenomena in space and time. Modern experimental innovations produce more complex and highly resolved data than ever before, which will continually require new analytical approaches. Some of the new approaches that were discussed during the workshop were:

    - *Low-dimensional representations of high-dimensional spatiotemporal data:* Using domain adapted basis functions to efficiently represent data through orthogonal polynomials and the graph Laplacian (explored by Jörn Dunkel and Elizabeth Jerison).

    - *Transfer entropy and information flows*: How a cell or animal interprets and responds to its environment is crucial for understanding their spatiotemporal dynamics. Thierry Emonet's talk introduced a new mathematical framework to explain these interactions using transfer entropy and information flows. This enables us to understand decision making in bacterial chemotaxis and olfactory navigation by considering both how environmental information flows to behavior and how behaviors feedback to environmental inputs. This feedback informs spatial dependencies in fruit fly navigation strategies.

    - *Data-informed dynamic potential landscapes:* Data can be used to understand development through a dynamic potential landscape model, an idea introduced by C.H. Waddington's "The Strategy of Genes". Several talks introduced new methods to understand this process. James Briscoe showed how a landscape can fit using concepts from Morse-Smale dynamical systems. These landscapes provide insights into the dynamics of developmental cell-fate decisions and inspire new verification experiments. Crucially, the talk highlighted how feedback informs correct predictions of the landscape's temporal dynamics. Gautam Reddy introduced a new control perspective on cell-fate decision-making that can be used to understand when the Waddington picture is valid, and what it might look like in practice.

    - *Model-free approaches*: Frequently in complex biological systems, underlying models are unknown. Jonathan Colen and Margaret Gardel introduced a model-free approach of using Fourier-based neural network methods to approximate dynamics in these cases. These networks are physically motivated by Green's functions, providing a physically motivated way to interrogate dynamics directly from data. Similarly, the seminar talk by Edouard Hannezo explained how graph neural networks can be used to interpret complex shape dynamics during morphogenesis.

Participant Feedback

An anonymous survey facilitated by the Northwestern University Program Evaluation Core reflected positive overall feedback. 100% of survey respondents said the workshop was worth their time, expressed interest in attending future NITMB workshops, and said they would recommend them to colleagues. 100% also reported that the workshop helped them better understand new scientific language they were not previously familiar with, and 97% expressed a higher degree of confidence in their ability to apply mathematical tools or concepts to biological questions. When asked about key takeaways, participants said the program helped expand their knowledge of different model systems and encouraged them to think about connected ideas across scales. 87% of respondents agreed that the workshop led to meaningful connections which they expect to continue beyond the workshop. Each participant reported an average of 2.7 newly formed connections, most commonly with scientists from other disciplines.

Feedback for improvement primarily focused on the discussion sessions, which some participants felt became talks by their volunteer leaders rather than open conversations. Suggestions included providing clearer guidance for discussion session leaders, gathering participant interests in advance, crowd-sourcing topics on the first day, and preparing questions to open each session.

Outcomes and Impact

As advances in experimental imaging continue, access to data at high spatiotemporal resolution will only continue to grow. As we saw in this workshop, such data pose new and unique challenges for theoreticians. This workshop synthesized key theoretical and experimental advances for probing spatiotemporal programs in biological function, ranging from subcellular to ecosystem-scale environments. The program enabled connections between geographically distant scientists, as well as researchers from disciplines who may not have been familiar with each other's work. This provided an outlet for theoreticians to gain methodology feedback from the experimentalists whose data could benefit from it, allowing theoreticians to make data-informed adjustments to their analytical pipelines. By bringing together researchers from experimental and theoretical frontiers, the workshop helped to inspire and motivate the development of analytical tools for tomorrow's data. The organizers will explore potential follow-up events to continue seeded collaborations.