What is Theoretical Biological Physics in
The Age of Quantitative Biology and Big Data? Workshop

Program Titles & Abstracts

OPENING DISCUSSION:

Ilya Nemenman, Emory University
“Is There a Place for Theoretical Biophysics?”

Abstract: This talk will attempt to frame the main discussion points for the workshop. To which extent has theoretical biophysics impacted our understanding of life in the recent decades? What have we done differently from biologists, chemists, and computer scientists? What have we achieved? I will argue that our recent progress has been slower than we had hoped. And this will bring me to the second set of questions: Why do we believe theoretical physics approaches should succeed in biology? Why do we want them to succeed at all, and how would success look like? Of course, I believe that our questions and our methods have a role to play. This will bring me to the third set of questions: What is missing from the traditional tool kit of theoretical physics to make an impact in modern high-throughput biology? and How do we harness computing and data to generate impactful theoretical insight?

SESSION 1:

Mehran Kardar
“Genome Organization by Loop Extrusion”

Yi Jiang
“Epigenetic Landscape: Statics, Dynamics, and Stochasticity”

Starting from exactly the same genetic materials, how cells turn out to be so drastically different and do different things, in both development and diseases, is a big question in biology. Waddington’s epigenetic landscape is an abstract metaphor often used to represent the relationship between gene activity and cell fates during development. I will discuss a few recent work that use this metaphor in very different but complementary ways to address cell fate transitions.

Andre Levchenko
“Complex Optimization on Complex Landscapes in Biological Function”

Biological systems have evolved to successfully match multiple and diverse inputs to multiple outputs, guiding the biological responses appropriate to changes in the environmental milieu. Large scale data collection has suggested that complex cellular responses might be understood in the context of lower-dimensional approximations. Nevertheless, it is also clear that cells can perform
multiple functions, raising the question of how the potentially multi-dimensional optimization problem can be implemented within biological systems. Recently, primarily through the work by Uri Alon’s lab, it has been suggested that many biological optimization problems can be understood through the prism of Pareto multi-optimality approaches. The approach appears to be very powerful, capable of accounting for the so-called generalist and specialist cell states in the context of complex tissues and other levels of biological organization. This approach also suggests important implications for the physical biology treatment of complex biological systems, and in particular the notions of energy landscapes and entropy production, as well as matching the information flow to assuming particular allowable states. In this presentation, I would like to review this body of work and link it to some of the current and future developments in biological physics approaches to various key problems in cellular and molecular biology.

SESSION 2:

Rustom Antia
“How Have Mathematical Models Contributed to our Understanding of the Basic Principles of Immunology”
I will first introduce the basic principles of immunology. I will then explain the elements of quantitative reasoning that helped generate these, including the clonal expansion (Burnett), affinity maturation (Kepler and Perelson), Dynamics of HIV (Perelson). I will Outline 3 key areas where models are currently helping advance our understanding: GOD (Generation of diversity), memory, responses to persistent infections

Aleks Walczak
“Prediction in Biological Systems”
I will talk about three examples from very different areas from biology where people have tried to combine data with theoretical ideas to learn something about how biological systems attempt to interact with the environment. In some cases this influences the behaviour of these systems, in other cases it effectively understanding the physical interactions makes it possible for us to predict the behaviour of the system. The examples will be from neuroscience, sensing and evolution. As you see, I really do not know what I will be talking about.

Daniel Weissman
“New Approaches to Microbial Evolutionary Genetics”
Abstract: How did present-day genetic diversity arise from ancestral populations? Evolutionary biology has traditionally had two frameworks for answering this question. The first, sometimes called population genetics, is mostly used for diversity within eukaryotic species, and assumes that recombination is very frequent with only limited barriers. The second, phylogenetics, is mostly used for diversity between eukaryotic species and among prokaryotes and viruses, and assumes that recombination is very limited. But researchers looking at large genomic datasets without pre-committing to one of these approaches have shown that the most microbial evolution follows a different pattern, in which recombination is frequent but there are also frequent, strong barriers, with dynamics that do not match the standard population genetics model. Some promising new ideas have been proposed, but we are still just beginning to develop a theory of microbial evolutionary genetics.
SESSION 3:

David Schwab
“Biologically Plausible Learning Algorithms”
In this talk, I’ll give an overview of recent work on the development of learning algorithms that respect constraints from biology. I’ll discuss why I haven’t worked in the area yet, and why it’s a fruitful avenue for future research.

Ila Fiete
“The Theory that Launched a Thousand Boats:
Neural Computation with Discrete and Continuous Attractors”
This is going to take the form of a review of a body of work spanning 20 years, with the presentation of 2 ideas for computation with discrete attractors and continuous attractors, then presentation of a bunch of experimental systems that were proposed as candidates, then much more recent work testing the ideas experimentally with modern datasets. It won’t be about my work (but 1-2 examples out of several might be….).

Leonid Mirny
“Folding and Self-Assembly”
Large-scale structures in the cell emerge as a result of collective action of many identical molecules (e.g. tubulins), or folding of long polymers (polypeptides, RNA, DNA etc) -- these can be thought of as The Folding Problems. Progress of the Protein Folding field in 1990s suggested physical principles governing robust self-assembly of heteropolymers (“the energy gap”, aka designed REM). The challenge in understanding large-scale assemblies is that the final ~1000nm-size structures depend on microscopic properties of individual (~1nm) molecules. Some progress has been made in bridging across scales, e.g. understanding the assembly of the mitotic spindle. Interestingly, while microscopic assemblies (e.g. protein/RNA folding) are driven by heteropolymer interactions, large-scale assemblies (cytoskeleton, chromatin) appears to be driven by active processes. Future research can aim to elucidate physical principles behind activity-based self-assembly/folding.

SESSION 4:

Herbert Levine
“Phenotypic Exploration as a Response to Cellular Stress”
Experiments on a variety of systems from yeast to cancer cells seems to indicate that cells can successfully overcome stress by finding novel phenotypes. The search for these novel phenotypes seems to be stochastic and seems to depend on plasticity in (among other things) chromatin organization. A recent paper (Freddolino, P. L., Yang, J., Momen-Roknabadi, A., & Tavazoie, S. (2018). Stochastic tuning of gene expression enables cellular adaptation in the absence of pre-existing regulatory circuitry. eLife, 7, e31867) proposes an interesting model of this type of process, assuming that feedback from cellular stress takes place through the metabolic system. This talk will discuss these ideas and the many open questions remaining regarding the proposed process.
SESSION 5:

Danielle Bassett
“Human Learning of Relational Patterns”
Motivated in part by these papers:


Robert Batterman
“Multiscale Modeling and Universality”
I will briefly talk about modeling of material properties using a mesoscale approach. An important philosophical question concerns explaining the (relative) autonomy of continuum models from details at atomic and molecular scales. The relatively new field of biophysics that studies active matter raises some interesting modeling challenges and I begin to address some of them.

Pankaj Mehta
“Taking High-Dimensions Seriously in Biology”
Biological systems often live in high-dimensional spaces. Microbial ecosystems often have thousands of species that all interact to give rise to community assembly. The gene networks underlying cell fate often consist of thousands of genes and proteins and regulating each other. The question I have for all of us is: Can we exploit this high-dimensionality to form statistical physics style models for complex biological phenomena? I will argue that one promising avenue for this is embracing the physics of disordered systems and high-dimensional random geometry.

Erik van Nimwegen
“Identifying Phenomenological Laws is an Underappreciated Theoretical Activity”
Abstract: In his lectures on physics Richard Feynman summarizes physics as consisting of essentially three phases. Given certain natural phenomena of interest, the first phase consists of finding experimental procedures that allow one to reproducibly measure well-defined quantities that can characterize these phenomena. The second phase consists of finding quantitative relationships between these measurable quantities, i.e. sets of phenomenological ‘laws’. Finally, the third and most glorious phase consists of then finding an underlying theoretical viewpoint that in one full sweep explains the entire set of phenomenological laws.
I want to question whether there is, within community of theoretical biophysicists, an unjustified focus on the third of these phases, and an undeserved tendency to consider the first and second phases as not really constituting ‘theory’. I will argue that finding appropriate sets of variables, i.e.
those that not only can be measured unambiguously, but capture the behaviors of the phenomena of interest and can be used to identify informative quantitative relationships, is often the most challenging aspect of doing theory in biology. I will mention a few example areas that I feel are strongly in need of phase 1 & 2 type work, and ask whether there would be ways to increase the appreciation of this kind of work, for example by better formalizing what constitutes ‘success’ in these areas.

SESSION 6:

**Gordon Berman.**

“Building Long Time Scales in Genes, Neurons, and Behavior”

Most scientific investigations involve a choice of scale — molecules, cells, or animals, quarks or bulldozers — typically because it is experimentally necessary to measure phenomena at particular spatial and temporal resolutions. As theoretical physicists, however, we often are most excited when our results explain how details on a smaller scale affect or do not affect details on a larger scale (e.g. the renormalization group in statistical physics). Such frameworks are largely lacking in organismal biophysics however. In animals, how are the striking dynamics and behaviors that we observe at long time scales created? Or perhaps this is the wrong way of framing the question, and perhaps we can best understand behavior by observing how long time scale dynamics in gene expression or neural activity biases behavioral output. Here, I will provide a brief overview of recent results in this area and will point towards open questions that theoretical biophysics is well-suited to explore.

**Andrea Liu.**

“Topological Nature of Structure-Function Relation in Flow and Mechanical Networks”

What, precisely, is encoded in the structure of a network that enables it to perform a function? The goal of protein structure determination is to identify the structure-function relationship. Similarly, the point of constructing the connectome is to understand how the brain works. Yet many proteins have the same folding structures and completely different functions, while others perform similar functions with entirely different folding structures. We have uncovered the structure-function relation in functional flow and mechanical networks, and it is simultaneously more subtle, more simple, more sensitive and more robust than one might have expected.

**Nigel Goldenfeld.**

“Is the Phenomenon of Life an Inevitable Consequence of the Laws of Physics? And why this Actually Matters!”

Despite the triumphs of molecular biology and the biomedical enterprise during the last century, there has been no progress in our understanding of why the phenomenon of life actually occurs at all. Is it simply some strange fine-tuned accident of carbon chemistry, or does it reflect deeper principles of the self-organization of matter under non-equilibrium conditions? I will pose this question sharply by comparing and contrasting the levels of description for our current understanding of life with superconductivity in materials science, along with their ensuing explanatory power. I will propose that a way forward is to try and understand what drives the open-ended growth of complexity, which I argue is one of the key epiphenomena of life, and will give what is perhaps the earliest attempt to demonstrate a dynamical system that exhibits this as an emergent feature. Lastly, I will suggest that this question is not “angels dancing on the head of a pin”, but is central to our inability to control evolving systems, ranging from bacterial infections, cancer tumors, weeds and insects, all of which have rapidly evolved resistance to our interventions. I will suggest one idea for how one could reconceptualize the way we manipulate such systems for societal benefit.