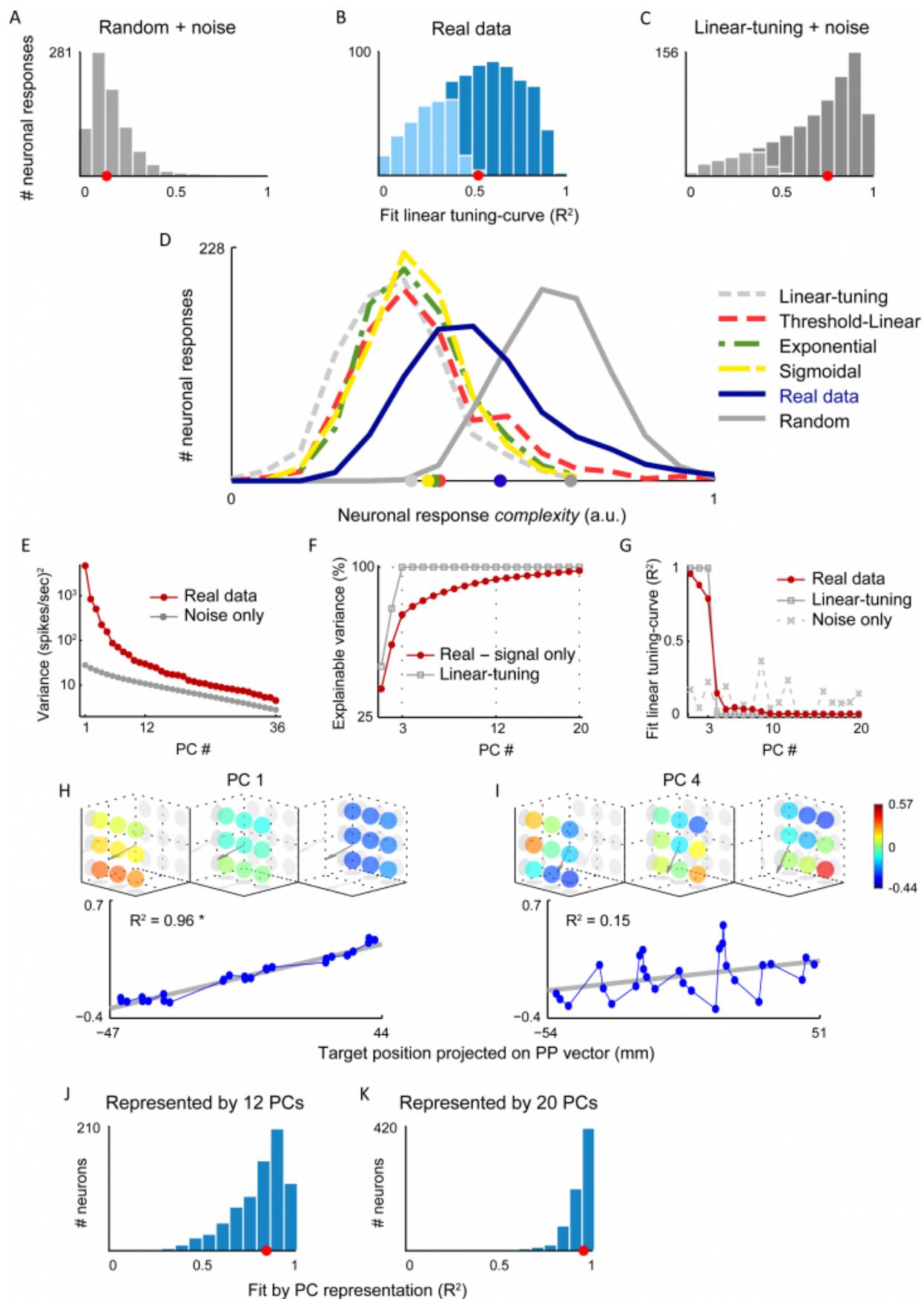


Why we need computational models in biology

August 1 2016, by Naureen Ghani



Many researchers begin the scientific process by making observations of the natural world and collecting data. They then try to extract patterns from these observations and data using statistical analysis. However, defining statistical correlations alone does not result in understanding. Instead, a theory is needed. A scientific theory aims to provide a unifying framework for a large class of empirical data to help researchers make testable predictions.

Although theory is celebrated in the physical sciences, it is questioned in the life sciences. Theory in biology was initially obscure and often relegated to highly technical journals. However, with the advent of big data, theory has now come to the forefront in biology. In this post, I will discuss the role of theory in biology, provide examples of important models, and conclude with an in-person interview with prominent theorist Larry Abbott at Columbia University.

Why Physicists Like Models, and Why Biologists Should

In biology, few quantitative theories are predictive, leading some scientists to distrust theoretical studies. In physics, the opposite is true. The difference lies in the nature of the systems being studied: while physics derives beauty from simple reductionist elegance, biology finds beauty in complexity and richness. For this reason, simple mathematical theories of biology are often incorrect. Many experimentalists also see simulated data as too far removed from biology. Some are frustrated by

the dense language of computational papers and inaccessible math used to explain straightforward biological principles.

I believe that computational models can complement experimental data to provide superior biological understanding and treatment of diseases. A good computational [model](#) inspires new experiments and provides new insights. While models cannot prove what mechanisms are at work, they can suggest what variables are most important to investigate in an experiment. Daniel Hillis compares the utility of theoretical models to that of model organisms: "models cannot prove anything conclusive about biological evolution anymore than the nervous system of a nematode can prove anything about the nervous system of a mammal." In other words, both computational models and simpler nervous systems serve as instructive examples.

Learning from Theory: The Discovery of DNA Structure

Theory played an important role in the discovery of DNA structure. While Francis Crick had a background in mathematics and physics, James Watson had expertise in the molecular biology of phage, the viruses that infect bacteria. Working together, these scientists used model building to reveal the famed double helix. X-ray crystallographic data obtained by Rosalind Franklin and Maurice Wilkins at King's College London were also crucial to the discovery. In particular, Franklin's photo of the B-form of DNA pointed to the helical structure of DNA. "The instant I saw the picture, my mouth fell open and my heart began to race," wrote Watson. Together, Watson and Crick built a now famous model of DNA using metal plates for nucleotides and rods for the bonds between them. The true beauty of this model is that structure implies function, and this discovery facilitated a new era in biological research.

Computational Models in Neuroscience

Computational models have become very popular in neuroscience, where the Hodgkin-Huxley model of action potentials is arguably the most important theory. This model is a set of nonlinear differential equations that approximates the electrical patterns of excitable cells such as neurons and cardiac myocytes. The Hodgkin-Huxley model has inspired contemporary neuroscientists like Professor Abbott to model firing patterns of cortical brain cells. In a PLOS Computational Biology paper, Abbott addresses the relationship between tuning curves and neural circuits. A tuning curve is a graph of auditory threshold intensity at different frequencies for a single neuron. As neurons have distinct tuning curves and are thought to arise from structured synaptic connectivity, a theoretical model can predict the order of synaptic inputs. Knowledge of the order of synaptic inputs, such as the identity, strength, and location of each synapse, is critical for understanding how neurons compute.

Professor Abbott on Creating Models

In a PLOS Computational Biology paper, Lalazar et al create a theoretical model for arm posture control in a primate monkey model. The results of this neural network model were compared to biological data obtained from the primary motor cortex area. Surprisingly, this study found that synaptic connectivity in this model is completely random.

Professor Abbott was a theoretical particle physicist at Brandeis University for ten years before he switched to neuroscience. Today, he is a leader in theoretical neuroscience and a co-author on the first comprehensive textbook on theoretical neuroscience. He was inspired to transition into biology after a visit to the laboratory of Professor Eve

Marder at Brandeis University. Mesmerized by the sound of spikes of electrical activity in neural tissue, Abbott trained with Marder for one year. They subsequently published together for over a decade.

At Columbia University, Abbott founded the Center for Theoretical Neuroscience. He collaborates extensively with experimental biologists including Eric Kandel. Abbott uses computer simulations and analytical techniques to model and analyze neural circuits that drive behavior. "I first try to take all the important features of a neural circuit and then see what they imply. I then see if they agree with what I believe are the important experiments," Abbott says during our interview. In other words, Abbott first determines the neurons that participate in a neural circuit. He then generates a simulation to predict how each neuron integrates input signals from synapses.

A good model will recapitulate biology and lead to novel understanding. However, a [computational model](#) in biology need not be predictive to be of use. "You can have models of a well-understood phenomenon if you describe it in a new way. These models will lead to greater understanding," Abbott says. He states that it is critical for a model to go beyond our simple intuition.

Learning Computational Skills

Abbott argues it is critical for early-career biologists to learn computational skills. "Knowing skills outside your field before you choose to specialize is really good. It's very hard to do it in the reverse order once you've picked a lab. Statistics and math are important skills today."

I can attest to the benefits of learning computational skills as I first trained in a mechanical engineering lab. When I entered the neuroscience field, I already understood the engineering behind

electrophysiology rigs and the math behind [theoretical models](#). In my current research, I merge experiments and [theory](#) using the simple nervous system of a fly, and this work has shown me the value of combining these two approaches. To move forward, I believe theoretical biologists and empirical biologists must make their work more accessible and valuable to each other. Professor Abbott is a testament to this type of collaboration and has succeeded in attracting mainstream attention to computational theories in neuroscience. Theory can provide novel insights and change the way experimental biologists understand their subject.

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