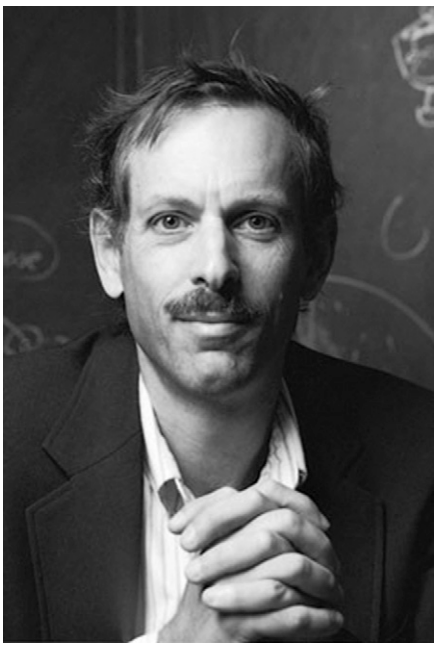
Profile of Eric D. Siggia

In the past two decades, microarrays, so-called omics technologies, and improved methods for nucleic acid sequencing have created a vast amount of biological data for researchers to sort through. Pioneering fields of science have sprung up in response to this challenge, eager to create helpful tools by leveraging the expertise of scientists in fields as diverse as mathematics and physics. Condensed matter physicist Eric Siggia, a recently elected member of the National Academies of Sciences, has been at the forefront of this movement.

In 1997, Siggia was one of only three physicists at The Rockefeller University in New York City to pursue biological research. Since then, he has applied his analytical expertise to a range of seminal biological questions, from the physical properties of DNA to gene regulation and embryonic development. Siggia ponders these questions with a holistic view that detects novelty in systems other scientists had long laid to rest. This perspective has allowed him to formulate innovative strategies for keeping pace with the deluge of data generated by what he calls the "too successful" field of genetics.



Eric D. Siggia.

Early Explosions

A New Jersey native, Siggia was born and raised near the rural Pennsylvania border. His father, an industrial chemist, stocked the family's bookshelves with math and science textbooks, and "having nothing else to do in cow country," the future physics professor recalls that he read. Even before his teenage years, Siggia had devoured basic chemistry and physics tomes and could converse about his father's work. The young Siggia developed a strong interest in the theoretical underpinnings of physics, cultivating a particular facility for mathematics. "The game or puzzle aspects of math always interested me," he admits. By the time that he had reached high school and his family had moved to Amherst, Massachusetts, Siggia took many of his classes at Amherst College.

Although the budding physicist could absorb textbook material, experiments proved trickier. Aided by his father, he managed to create a gas chromatograph, but other projects ended in flames. "There were various explosions and smelly mixtures in the basement—we weren't too systematic," Siggia recalls.

Oddball Investigations

In the fall of 1967, Siggia entered Harvard College. He soon dove into graduate work and became a student of theoretical physicist Paul Martin, who Siggia recalls was "easy to find, as he was the only physicist at Harvard not doing high-energy physics at the time." Five years after entering the Cambridge, Massachusetts institution, Siggia graduated with a doctorate in physics, completing his thesis on fluid turbulence (1). He stayed in Cambridge for 3 additional years supported by a prestigious Junior Fellowship. The program, developed by former Harvard President A. Lawrence Lowell in 1933, frees young academics from the constraints of working within one particular department and allows them to pursue "oddball things," says Siggia.

With Bert Halperin and Pierre Hohenberg, then of Bell Laboratories, Siggia studied the dynamics of second-order phase transitions using a mathematical device known as a renormalization group that had been recently developed by Ken Wilson of Cornell University. Wilson would later earn the 1982 Nobel Prize in Physics. Renormalization groups allow systematic investigations of physical systems at differing scales. "These changes of state," Siggia explains, "have a surprising property. Fluctuations are scale-free and have universal, material-independent exponents—for example, a magnet and a fluid show the same behavior quantitatively" (2).

Structured Turbulence

After a brief stint at the University of Pennsylvania, Siggia left in 1977 to join the physics faculty at Cornell University. The upstate New York university was home to several prominent condensed matter physicists, including Wilson and Michael Fisher, who studied critical phenomena, and Robert Richardson and David Lee, who would win the 1996 Nobel Prize for their work on superfluid helium. "Cornell was clearly preeminent without a close second, so I was glad to join," Siggia recalls. There, he met his wife, prominent political theorist Susan Buck-Morss.

At Cornell, Siggia studied the mechanics of fluid turbulence from a theoretical perspective. His research focused on phenomena like the wakes that occur when boats cut through bodies of water. These wakes, Siggia found, appear to create regular and highly structured flows behind them as the displaced liquid radiates out. "The puzzle to solve was how these structures give rise to the smooth profiles we see," Siggia explains. Numerical simulations run on early Cray supercomputers allowed him to visualize these structures in other flows that statistically have no preferred direction (3).

He continued collaborating with researchers at Bell Laboratories such as Boris Shraiman, now of the Kavli Institute for Theoretical Physics at the University of California at Santa Barbara. Together, they investigated an aspect of fluid turbulence called scalar turbulence—a phenomenon that many have felt but few know by name. "If you've ever lain on the beach, you've felt its effects," Siggia says. "You have hot sand on the beach, and you have a breeze flowing over the ocean, coming into shore. You would think that turbulence would mix everything, but instead, you feel rather abrupt steps in temperature," Siggia explains. Previous theories could not account for this phenomenon, and Siggia and Shraiman developed a quantitative model for scalar turbulence (4).

Magnetic Superconductors

Siggia's collaboration with the Bell researcher proved fruitful; together, Siggia and Shraiman investigated the properties of high-temperature superconductors, which had been discovered in the mid-1980s at the IBM laboratories in Zurich. One puzzling aspect of these materials, in addition to their high superconducting temperatures of over 90 K (−183 °C), was the magnetic properties of the parent compounds. Magnetism and superconductivity were supposedly antithetical according to BCS theory, named for the three researchers—John Bardeen, Leon Cooper, and John Robert Schrieffer—who first offered the explanation of low-temperature superconductors in the late 1950s. Siggia and Shraiman looked into the magnetic properties of a subclass of high-temperature superconductors and calculated how they simultaneously

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 5568.

carried an electric current but retained their underlying magnetic order (5).

Pulling DNA

During this time, Siggia began to find biological applications for his research. Although the transition might seem unusual, Siggia claims it was anything but unusual. "It came through an interest in biophysics," he explains.

After attending a talk on DNA manipulation by Carlos Bustamante of the University of California at Berkeley, Siggia and former postdoctoral fellow John Marko, now at Northwestern University, analyzed the force extension of dsDNA. By borrowing the so-called "wormlike chain model" from polymer physics, the pair developed an elegant expression for the mechanical properties of dsDNA that was sequence-independent and agreed with experiments (6).

"That at the time was a bit of a surprise," Siggia notes. "It was certainly an example of a type of physical phenomenology applied to a biological problem. People in the biophysical arena didn't quite do these types of calculations, and they have proven extremely useful." The research helped pave the way for studies on the mechanical properties of biologically relevant molecules from DNA processing enzymes to protein motors that package viral capsids.

Scientific Shift

While on a short sabbatical from Cornell in 1996, Siggia met cell biologist Jennifer Lippincott-Schwartz at the National Institutes of Health. "In contrast with almost everything else in the field, Lippincott-Schwartz was imaging live cells," he notes, and his own research began turning more heavily to the biological sciences. Siggia quantified the movies generated by the National Institutes of Health scientist's laboratory, which tracked nuclear membranes during mitosis and Golgi tubule trafficking among other in vivo experiments. (7, 8) "We treated these live cell images as dynamic systems on which you could do physical chemistry."

Siggia's transition from working on quantum mechanical problems to biological ones paralleled a greater scientific movement in the mid-1990s. At The Rockefeller University, then President Torsten Wiesel recognized the role that physicists and mathematicians could play in biological research. This realization served prescient with the coming systems biology era, and Wiesel encouraged the hiring of quantitative specialists with interests in biology.

After nearly two decades at Cornell, Siggia accepted a position as professor of physics at The Rockefeller University, where he continues to explore complex biological questions.

Genomic Algorithms

In the late 1990s, as Siggia moved into his office that overlooks the East River, researchers published the first complete genome of a eukaryotic organism—the yeast *Saccharomyces cerevisiae* (9). The rush to analyze this wealth of information revealed genes crucial to the yeast life cycle. Siggia, however, took a step back and used a statistical approach to identify elements that controlled the expression of these genes. As he saw it, the question was clear, if not easy to answer: "Here's this genome. Can you compute the regulation?"

With colleagues at The Rockefeller University, Siggia developed an algorithm that analyzed yeast DNA for sequence patterns in known regulatory regions. Intriguingly, they first tested the predictive power of their code on the classic Herman Melville tale *Moby Dick*. They took the complete text of the novel, removed punctuation and capitalization, and turned it into a string of letters representative of an unspecified genome. They gave the algorithm, which was initially named after the novel, a set of probabilistic rules so that it could build common word fragments and then reconstruct an English lexicon. "It was surprisingly good and easily found words like whaling and even names like Queequeg. So what you think is odd is actually easy—since it's improbable," Siggia adds.

With a new set of rules, the researchers trained the Moby Dick algorithm and its descendants, which they named Ahab and Stubb, to find regulatory elements in the yeast and then fly genomes (10). Their method differed from more popular approaches to determine gene regulation, in which researchers examined clusters of coexpressed genes for their common regulatory element.

New Approaches to Old Paradigms

Siggia's tenure at The Rockefeller University has spun off other productive collaborations. With geneticist Fred Cross, he has helped revise our understanding of how cells commit to another round of cell division. The pair of researchers combined single-cell imaging with an analysis of genetic perturbations that had only been characterized at the population level, uncovering a cyclin-mediated feedback loop that defined the commitment point of yeast cell division and lead to a bistable state (11). Siggia's Inaugural Article also elucidates development in another model organism in biology, the nematode *Caenorhabditis elegans* (12). He views the article as a "manifesto of sorts," because it espouses a way for scientists to account for phenotypes quantitatively rather than as collections of gene products. "Even when you think you have identified every gene that contributes to a particular phenotype, next year, somebody will find a new gene, and yet, the phenotype hasn't changed."

As Siggia notes, "during development, if you look at how cells transform themselves, it is a time-dependent process. And genetics, even if successful, does not really give you time-dependent information. So, if one really wants to think about development and be quantitative, dynamic models guided by geometric reasoning, can be a very useful intermediate step and may be a final step, because they're also predictive." Siggia hopes to apply this methodology to vertebrate development as well.

Although he hesitates to predict what the next 5 years will hold—just as he could never have predicted his trajectory from physics to systems biology—Siggia remains content to marry seemingly disparate scientific disciplines. "I've been able to take quantitative people from physics, applied math, and computer science and introduce them to contemporary biology," he says.

For the physicist, the scientific question always takes precedent over the method used. "I try to make the people who come through my group deal with problems first and tools second," he says. "Biology is not an excuse for doing physics with the names on the variables changed—there are too many interesting questions."

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