PROFILE

Profile of Edward H. Egelman

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Edward H. Egelman has had a long and distinguished career as a biophysicist, but he took a fairly circuitous path into science. Egelman graduated high school in 1968, a particularly tumultuous year for the United States. "This was the peak of the Vietnam war and my main interests at that point were focused on opposition to the Vietnam war and issues of social justice, racism, and inequality," he says. After starting an undergraduate degree at Brandeis University, Egelman dropped out and was actively involved in the antiwar movement.

When Egelman eventually went back to Brandeis, an interest in philosophy led him to pursue a degree in physics. "I thought that maybe physics held the answer to all these interesting philosophical questions," he says. After completing a physics major within a year and a half and graduating in 1976, Egelman started a doctorate in experimental high-energy physics at Harvard University. "I quickly became pretty disillusioned with that type of physics; it was sort of industrial scale with [dozens of] authors on each paper," he says.

As he considered his next steps, Egelman recalled enjoying his undergraduate honors research project with David DeRosier, whose work lay at the intersection of physics and biology. "I had so much fun doing that project, and I thought perhaps biophysics might be as much fun," he says. Egelman returned to Brandeis to work with DeRosier for his doctorate in biophysics. "In biophysics, a person could do something on a benchtop that was both interesting and potentially relevant to public health," says Egelman. "Everything I've done since then is sort of a continuation of that work," he says.

Edward H. Egelman. Image credit: UVA Health/Kay Taylor.

During his career, Egelman has deciphered the structure and function of protein polymers and has made key contributions to the use of cryoelectron microscopy. He has used high-resolution imaging to study actin polymers, bacterial structures called pili that are essential for pathogenesis, and viruses that infect bacteria living in hot and acidic conditions; the latter feature prominently in his Inaugural Article (1). Now a professor of biochemistry and molecular genetics at the University of Virginia in Charlottesville, Egelman was elected to the National Academy of Sciences in 2019 for his discoveries in biophysics and structural imaging.

Studying Filament Structures

During his doctorate, Egelman studied the structure of actin filaments, which play an important role in a wide range of cellular processes, including muscle contraction, cell motility, and cell division. This work led Egelman to develop methods for the high-resolution structural studies of many other polymers. "One of the papers I'm most proud of I did as a graduate student," he says. "It involved determining the diffraction of filaments with variable twist, and to me this was really elegant because it could be reduced to a few simple equations," says Egelman (2).

Following his doctorate, Egelman joined the Medical Research Council Laboratory of Molecular Biology in Cambridge, United Kingdom. After hearing a seminar talk, Egelman began to work on a genetic recombination protein—RecA—from bacteria that also forms helical filaments like actin. "These were very flexible filaments, very variable in structure, and what grew out of working on those was methodology for more generally reconstructing helical polymers in three dimensions," says Egelman.

Those were early days for structural studies, and new approaches were sorely needed. "The state of the field then was sort of what I refer to as 'the Dark Ages' of electron microscopy, because the resolution was so abysmal," says Egelman. "We actually didn't have computer graphics for most of the things that we did, so we built physical models and photographed them to sort of show what these structures looked like," he says.

The technical challenges of the time, however, did not deter Egelman from finding new ways to decipher polymer structures. "I think the advice I got early on about perseverance is very important," he says. "It

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frequently takes a thick skin and an enormous amount of perseverance to be successful in science."

Major Technological Advances

Egelman has witnessed and contributed to dramatic improvements in electron microscopy over the course of his career. The first 3D reconstruction by electron microscopy was published by DeRosier and Klug in 1968 (3); the resolution was around 35 Ångstroms. "We actually went back a couple of years ago and redid that system at 3.4 Ångstroms resolution, and that's about a 1,000-fold increase in information content," says Egelman. "Now we routinely achieve that type of resolution," he says.

Such technological advances have opened up new applications. "Back in the old days, basically the only thing you could really do with electron microscopy reconstructions was to dock in crystal structures that had been solved at high resolution," says Egelman. "The whole field was what we referred to as 'blobology,' because you could only describe the different blobs, and relating that to function was almost impossible," he says. "In contrast, in some of our recent publications we've actually been able to even determine the protein sequence from doing the electron microscopy," says Egelman.

During this period, Egelman figured out many polymer structures while continuing to contribute to the field's technical advances, culminating in the development of an algorithm that is now widely used in cryoelectron microscopy. "Around the year 2000, I developed this approach for helical reconstruction that is now basically being used around the world [in] electron-microscopic reconstruction of helical polymers," he says (4). "That just opened up this enormous opportunity to begin looking at many other filaments, many of them. . .important in issues of health."

Bacterial, Archaeal, and Viral Filaments

Equipped with higher-resolution techniques, Egelman began to study structures called pili, which emanate from the surface of bacteria. Understanding the basic biology of pili could provide a foundation for the development of therapeutics or drug targets. "These structures are essential virulence factors, because if pathogenic bacteria don't express these pili, they're relatively harmless as they can't attach to the host cells and therefore can't mount an infection," he says. "The first one we looked at was from *Neisseria gonorrhoeae*, the bug responsible for the sexually transmitted disease," says Egelman.

Egelman also developed an interest in the pili of organisms living in extreme environments, such as those of archaea that live in nearly boiling acid and whose pili are evolutionarily related to bacterial pili. It turned out that viruses often infect archaea by binding to their pili. This prompted Egelman to begin studying the structure of archaeal viruses as well, in collaboration with David Prangishvili, who recently retired from the Institut Pasteur in Paris.

"These seemed like such incredibly interesting specimens to look at because they're very, very simple," says Egelman. "In some cases the virus is almost entirely thousands of copies of a single relatively small protein and DNA, and the interesting question is how these proteins can protect the DNA in such an extreme environment," he says.

Living organisms typically have active mechanisms to repair DNA, but viruses lack such mechanisms. "So the question is how viruses can accomplish this protection of DNA in a totally passive manner," says Egelman. "That gets to the Inaugural Article, which is focused on these viruses that infect organisms in nearly boiling acid." To Egelman's surprise, his research into how viruses protect their DNA would harken back to some of the earliest findings about DNA structure (1).

Unexpected Form of DNA

When Rosalind Franklin generated the first X-ray diffraction patterns of DNA in the 1950s—the ones used by Watson and Crick to build their models of DNA structure—she found two different types of structures. There were highly ordered structures formed by drying down the DNA in the laboratory, which Franklin called the "A" form. Rehydrating this DNA resulted in a different, much less ordered pattern, which she called the "B" form.

"The first virus we looked at, the very exciting finding was that the DNA was being maintained in the A form," says Egelman. "The prevailing idea in biology has been that the A form of DNA visualized by Rosalind Franklin was a laboratory artifact, but it turns out that's not true" he says.

Keeping DNA in the A form may help viruses protect it. "Some of the DNA damage caused by radiation involves hydrolysis of the DNA backbone," says Egelman. "So, if you're removing water molecules, the DNA may be much less susceptible to certain types of radiation damage," he says. In addition, UV light can also damage DNA by causing the formation of pyrimidine dimers, but the A form of DNA may have a much lower ability to form such dimers. "So there are a number of reasons why that A form is going to be a protective storage form," says Egelman.

Egelman also found structural similarities between archaeal viruses. "What was surprising was that we found these different viruses in different parts of the world that have unrecognizable sequence similarity and, in some cases, were believed to be parts of very different viral families. But, in fact, they have the same 3D fold of their proteins and clearly have common ancestors," he says. "So the structural studies provide much greater sensitivity for looking at evolutionary relationships than we can get from just looking at sequences," says Egelman.

The findings in Egelman's Inaugural Article (1) have implications for understanding virus evolution. "In virology there has been a basic assumption that membrane-enveloped viruses, like influenza or Ebola, are very different from nonenveloped viruses," says Egelman. "What we're able to show in these structural comparisons is that some of the membrane-enveloped viruses are extremely similar to the nonenveloped

viruses, so the gain or loss of membrane covering has been a much more recent adaptation," he says.

Egelman hopes to characterize many more viruses in extreme environments. "It would be really nice to extend our present work to show that one could find potential intermediates between some of these structures, given that they all must have common ancestry," he says. Understanding these structures could have intriguing applications as well. "There's just an infinite range of what you could do with these structures, and they could be used for everything from drug delivery or medical imaging to platforms for vaccines," he says. "You're just limited by your imagination."

Despite his decades spent trying to better understand polymer structures, Egelman's motivation remains undimmed. "It's been fascinating, because although we know so much more now than we did, there's still so many questions that we still can't answer," he says.

1 F. Wang *et al.*, Structures of filamentous viruses infecting hyperthermophilic archaea explain DNA stabilization in extreme environments. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 19643–19652 (2020).

2 E. H. Egelman, D. J. DeRosier, The Fourier transform of actin and other helical systems with cumulative random angular disorder. *Acta Crystallogr. A* **38**, 796–799 (1982).

3 D. J. DeRosier, A. Klug, Reconstruction of three dimensional structures from electron micrographs. *Nature* **217**, 130–134 (1968).

4 E. H. Egelman, A robust algorithm for the reconstruction of helical filaments using single-particle methods. *Ultramicroscopy* **85**, 225–234 (2000).