Limits and progress

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In 1998 I received an email from the late biophysicist Klaus Schulten. He had heard a talk on a promising technique for imaging biological samples and urged me to write about it in PHYSICS TODAY. Other experts were just as enthused. My story, "Electron cryomicroscopy comes of age," appeared in the magazine's March 1999 issue.

Back then, cryo-EM—to use the technique's catchy abbreviation—had yielded just three biomolecular structures at atomic resolution: the protein pump bacteriorhodopsin, the light harvester LHC II, and the molecular building block tubulin. Now the total stands at around 5000. Although I had kept up with progress in cryo-EM, I was nevertheless awed by what I learned at this year's annual meeting of the American Crystallographic Association in New Orleans.

To pick just one example, Shigeki Watanabe of Johns Hopkins University told attendees how he and his collaborators used cryo-EM to elucidate how neurons are able to sustain the transmission of signals across synapses. The question is puzzling because the transmission entails the release, within 100 ms, of glutamate and other neurotransmitters from tiny packages called vesicles that reside within the terminus of a neuron's axon. Given that the vesicles are ruptured with each neural firing, they must be regenerated and replenished rapidly.

To probe that process, Watanabe genetically engineered mouse neurons to include a light-activated sodium channel. He then used an LED to trigger, at a precise time, a neuron's firing while the cell underwent cryo-immobilization. By taking images at different delay times, he could catch the vesicles in the act of regeneration. From his flipbook of cryo-EM images, he discovered that new vesicles are created by pinching off a piece of the membrane at the axon terminal. Replenishing them with neurotransmitters occurs, rapidly and surprisingly, on larger structures known as endosomes.[1]

How has cryo-EM made such fast progress? My history of science friends would point to social and economic factors. Because of its importance to medicine, structural biology is well funded. Because structural biology is well funded, equipment manufacturers are motivated to improve their products. Indeed, many of the most recent leaps forward in cryo-EM have resulted from new, more sensitive electron detectors. (See PHYSICS TODAY, August 2016, page 13.)

But I suspect another reason is at play. In an influential 1995 paper, Richard Henderson of Cambridge University laid out the physical limitations of using electrons, x rays, and neutrons to probe molecular structure.[2] To biophysicists reading the paper, the promise of electron microscopy would have been evident and enticing. The earliest structures fell well short of Henderson's ideal performance, but there were no obvious impediments to dissuade cryo-EM pioneers and their successors from pressing on.

Exploring and delineating fundamental physical limits has a rich and fruitful history. Werner Heisenberg, for example, illustrated his uncertainty principle by working out an electron microscope's ultimate resolution. In elucidating the energetic limits of logical operations, Rolf Landauer and others paved the way toward the concept of reversible computing.

Sometimes the extent to which an idea can be pushed is not limited by a formula, or at least not one that anyone has derived. The first visible-light LEDs were red and made from gallium arsenide. One path toward blue LEDs was seemingly straightforward: Pair Ga with nitrogen, a lighter element from the same group as As. Nitrogen's smaller size yields tighter binding and, with it, a wider bandgap and shorter wavelength.

Nick Holonyak's red LED made its debut in 1962. Shuji Nakamura's blue LED appeared in 1993, after he, Isamu Akasaki, and Hiroshi Amano had spent decades figuring out how to solve myriad practical problems in achieving GaN's promise.

We don't know the highest temperature at which superconductivity can occur. If theorists ever determine the limiting T_c, reaching it will likely require imaginative, dogged experimenters and robust, sustained funding.

References

1. S. Watanabe et al., *Nature* **515**, 228 (2014).
2. R. Henderson, *Q. Rev. Biophys.* **28**, 171 (1995).

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