Reimagining electron microscopy: Bringing high-end resolution to lower-cost microscopes

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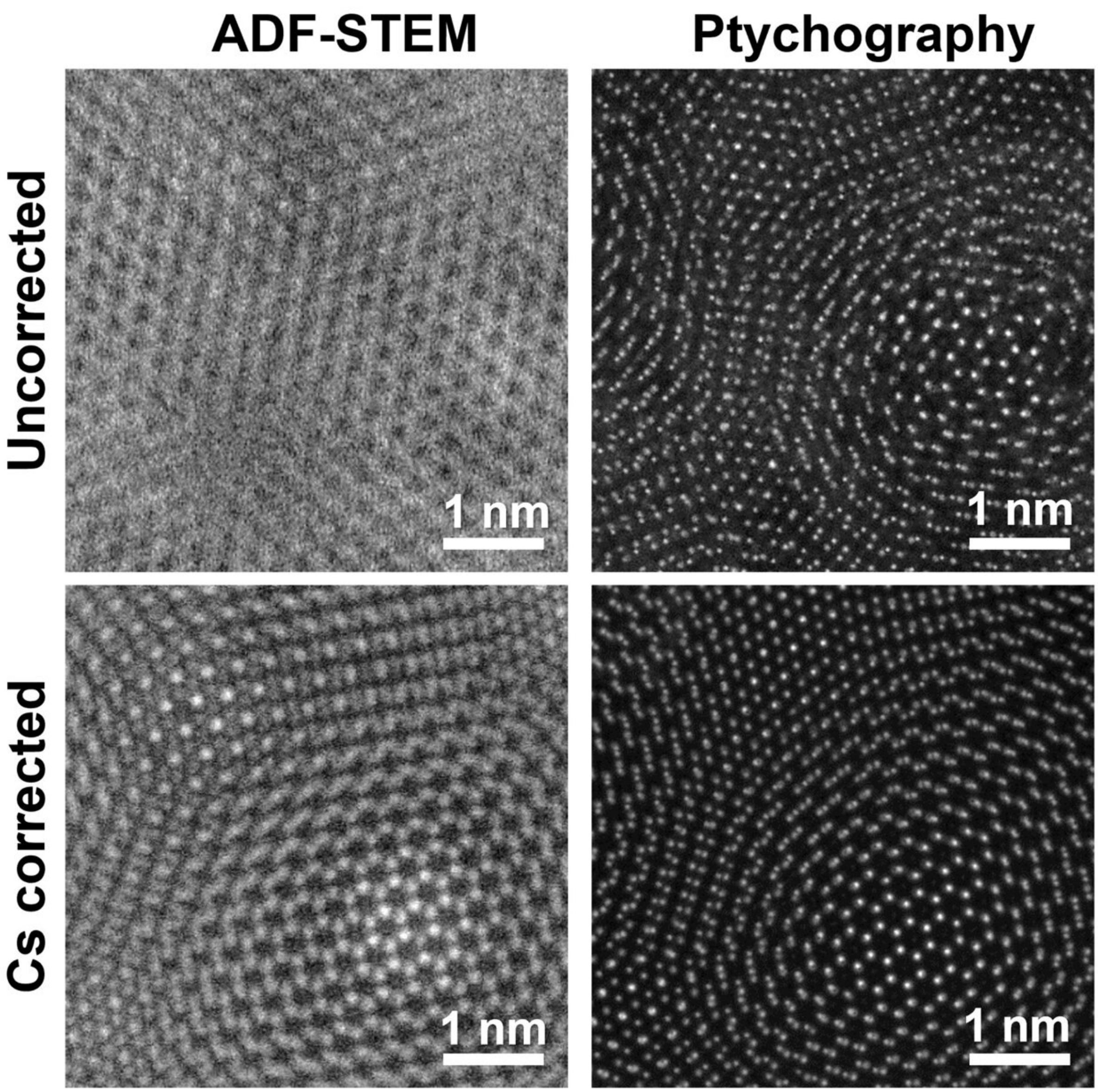

A comparison of experimental annular dark field (ADF)-scanning transmission electron microscopy (STEM) and electron ptychography in uncorrected and aberration-corrected electron microscopes. In the ADF-STEM image from the uncorrected STEM (top left), the resolution was sufficient to visualize the lattice of the sample but too poor to resolve individual atoms. In contrast, the ptychographic phase image (top right) resolved individual atoms. Measurements were repeated using aberration corrected-STEM. Both the ADF-STEM (bottom left) and ptychographic phase images (bottom right) resolved single atoms. The resolution achieved with electron ptychography in the uncorrected stem (top right) was nearly identical to the ptychographic resolution in the aberration-corrected microscope (bottom right) and readily exceeded the resolution of aberration-corrected ADF-STEM (bottom left). Credit: The Grainger College of Engineering at University of Illinois Urbana-Champaign

Researchers at the University of Illinois at Urbana-Champaign have shown for the first time that expensive aberration-corrected microscopes are no longer required to achieve record-breaking microscopic resolution.

The field of microscopy is in the middle of a great revolution. Since the 1800s and the invention of the compound light microscope, there have only been a few major jumps in resolution to see different length scales: from bacteria and cells, to viruses and proteins, and even down to single atoms.

Generally, as resolution has been making these incredible jumps, so has the price of the microscopes used to achieve that resolution. Such hefty price tags severely limit the accessibility of these instruments. The current jump in resolution comes from a new technique called electron ptychography—a method that uses computation to boost the resolution of electron microscopes—which has taken the field by storm in the last 5-6 years.

Researchers at the University of Illinois Urbana-Champaign have demonstrated record-breaking resolution using electron ptychography on "conventional" transmission electron microscopes (conventional meaning without expensive aberration correctors). This breaks the trend of increasing microscope price with increasing resolution. They were able to achieve deep sub-angstrom spatial resolution down to 0.44 angstrom (one angstrom is one ten-billionth of a meter), which exceeds the resolution of aberration-corrected tools and rivals their highest ptychographic resolutions.

"For the last 90-100 years, our field has thought that the way to do great microscopy is to make better and better microscopes," says materials science & engineering professor Pinshane Huang, who led this work. "The most exciting thing about our research is that we're showing that you don't need a cutting-edge microscope to make this work. We can take a 'conventional' microscope and do the same thing, using ptychography, and it's just as good! This is amazing because there can be a multi-million-dollar difference in cost between the two setups."

This research, co-first authored by former MatSE UIUC postdoctoral researcher Kayla Nguyen, former MatSE UIUC graduate student Chia-Hao Lee and Argonne National Laboratory staff scientist Yi Jiang, was recently published in the journal *Science*.

Before ptychography, the highest resolution electron microscopes used a technology called aberration-correction to allow scientists to see individual atoms. Rather than using a beam of light to probe a sample, electron microscopes use a beam of electrons, focused by electromagnets.

Electrons have wavelengths thousands of times smaller than visible light, which allows electron microscopes to resolve objects that are many times smaller than can be seen with optical microscopes. Scientists use these microscopes to decode the structures of objects ranging from the spike protein on the COVID-19 virus to the arrangements of atoms in graphene and, more generally, to peer inside matter to understand its atomic structure, composition and bonding.

However, one of the challenges of using beams of electrons is focusing that beam. "It's impossible to make a perfect lens for electrons," Huang says. "What people have been doing to compensate is making 'bad' lenses, and then putting aberration correctors after them, which are a series of 'bad' lenses that are 'bad' in opposite ways. Summed together, they make 'okay' lenses, and that's been the gold standard for how we image at the atomic scale for at least 20 years."

In optics, an aberration is any way that a lens deviates from a perfect lens. For example, human eyes can have several types of aberrations such as short- and near-sightedness (eyes can't focus at all distances) and astigmatism (curvature of the eyeball that causes blurred vision).

Lee explains, "For electromagnetic lenses, the way to focus these electrons is through an electromagnetic field. But we don't have a great way of controlling the shape and the strength of the electromagnetic field, which puts a very strong limitation on how precise we can be focusing these electrons."

In aberration-corrected microscopy, the current cutting-edge technology, there is an extra stack of lenses to correct the aberrations from the regular lenses, that changes the shape of the beam before it hits the sample. Those extra aberration-correcting lenses are where significant costs are added to the microscope.

While it is impossible to make a perfect lens, the goal of the last 100 years has been to continuously make better lenses to minimize aberrations. But Huang says, "What's exciting about ptychography is that you don't have to make better and better lenses. What we can do instead is use computers."

Rather than using a stack of lens optics to remove aberrations, ptychography removes them computationally. With a new generation of detectors, called hybrid pixel detectors, that cost a few hundred thousand dollars (compared to aberration-corrected microscopes that cost up to $7 million) and computer algorithms, this method can double, triple or even quadruple the resolution of what a microscope can achieve with its physical lenses.

Huang and her team have shown that their approach quadruples the resolution of conventional transmission electron microscopes. Further, nearly any scanning transmission electron microscope can now be adapted to achieve state-of-the-art resolution at a fraction of the cost.

While this approach is game-changing, Huang notes that ptychography is still a challenging technique that requires a lot of computation power. It can take hours to get a single reconstruction to reach the best resolution. But, as with many other technologies, computation advances quite rapidly and gets cheaper, faster and easier to use.

"We brought a cutting-edge technique, electron ptychography, to conventional transmission electron microscopes to show for the first time that a 'mediocre' microscope can do just as well as the most expensive microscopes on the market," Huang says.

"This is significant for the hundreds of institutions across the country and across the world who previously couldn't afford the cutting edge. Now, all they need is a detector, some computers and electron ptychography. And once you do that, you can see the atomic world with much more detail than anyone imagined even 10 years ago. This represents a huge paradigm shift."

More information: Kayla X. Nguyen et al, Achieving sub-0.5-angstrom–resolution ptychography in an uncorrected electron microscope, *Science* (2024). DOI: 10.1126/science.adl2029

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