Transmission electron microscopes use electrons with wavelengths of a few picometers, potentially capable of imaging individual atoms in solids at a resolution ultimately set by the intrinsic size of an atom. However, owing to lens aberrations and multiple scattering of electrons in the sample, the image resolution is reduced by a factor of 3 to 10. By inversely solving the multiple scattering problem and overcoming the electron-probe aberrations using electron ptychography, we demonstrate an instrumental blurring of less than 20 picometers and a linear phase response in thick samples. The measured widths of atomic columns are limited by thermal fluctuations of the atoms. Our method is also capable of locating embedded atomic dopant atoms in all three dimensions with subnanometer precision from only a single projection measurement.

Transmission electron microscopy (TEM) plays critical roles in the study of micro- and nanostructures in many fields, including physics, chemistry, structural biology, and materials science. Progress in aberration-corrector optics for electron microscopes has substantially improved the quality of the imaging system, pushing the spatial resolution to the sub–50-pm level. Nevertheless, in practical samples, this resolution limit is achievable only in extremely favorable conditions. One major obstacle is that multiple electron scattering is unavoidable in samples thicker than a monolayer, owing to the strong Coulomb interaction between the beam electrons and the electrostatic potentials from the atoms. Multiple scattering changes the beam shape within the sample and leads to a complicated intensity distribution at the detector plane. Nonlinear or even nonmonotonic contrast dependences on the sample thickness occur when imaging samples thicker than a few dozen atoms, which hampers direct structure determination by phase-contrast imaging. Quantitative structure-image interpretation usually relies on intensive image simulations and modeling. Direct retrieval of the sample potential requires solving the nonlinear, inverse problem of multiple scattering. Efforts have been made through different approaches, most of which are based on Bloch wave theory, by phasing different Bragg beams of crystalline samples. Unfortunately, these approaches become extremely difficult to implement for general samples with large unit cells or aperiodic structures, because a large number of unknown structure factors needs to be determined.

Ptychography is another phase-retrieval approach that dates back to Hoppe’s work in the 1960s. Modern, robust setups use multiple intensity measurements—usually a series of diffraction patterns collected by scanning a small probe across the extended sample. No periodicity or symmetry constraints on the sample structure are required as a priori knowledge. This approach has been widely used in the visible-light imaging and x-ray imaging communities. Until recently, electron ptychography has been constrained by sample thickness and the limited detector performance in electron microscopy. Two-dimensional (2D) materials and the development of direct-electron detectors have led to a wider renewed interest. Electron ptychography for thin samples, such as 2D materials, has achieved an imaging resolution of 2.5 times the diffraction limit of the lenses, down to a 39–pm Abbe resolution. However, such super-resolution approaches can be applied reliably only to samples thinner than a few nanometers, and the resolution in thicker samples is not substantially different from that attained with conventional methods. Such thin samples are practically difficult to achieve for many bulk materials, which currently restricts applications to 2-D-like systems, such as twisted bilayers. For samples thicker than the probe’s depth of focus, multislice ptychography, using multiple slices to represent the sample, has been proposed. The structures of all slices can be retrieved separately. There are several successful demonstrations of multislice ptychography using either visible-light imaging or x-ray imaging. Owing to experimental challenges, however, only a few proof-of-principle multislice electron ptychography demonstrations have been reported and are limited in either resolution or stability.

We demonstrate multislice electron ptychographic reconstructions experimentally, recovering a linear phase response versus thickness, and push the lateral resolution close to the intrinsic atomic size, limited by thermal fluctuations of the atoms themselves. The experimental setup is shown schematically in Fig. 1A. A defocused electron probe is raster-scanned across a slabslike sample, with one electron diffraction pattern recorded at each probe position by a high–dynamic range pixel array detector (fig. S1) (23). For thick samples, the probe function within the sample changes shape as a result of both wave propagation and strong dynamical scattering. A profile of the probe’s evolution with depth into the sample is shown in Fig. 1B. In conventional ptychography, we approximate the wave function at the exit surface of the sample as a multiplication of the incident wave function with a single projected sample function. For thick samples, however, portions of the sample at different depth positions are effectively illuminated with different wave functions as a result of beam spreading by diffraction. Following the well-known Cowley-Moodie multislice solution of the electron dynamical scattering problem, the sample can be considered as many thin slices until each slice satisfies the multiplicative approximation. The entire scattering procedure is modeled as sequential scattering from each slice followed by a free-space propagation to the next slice. For the inverse problem, a similar multislice procedure can be adopted on each iteration, as in multislice ptychography. In this work, there is no a priori assumption about the sample structure, and reconstructions start from random initial phases for all slices. The specimen potential for each slice is separately recovered through the phase of the transmission function, as illustrated in Fig. 1C.

We first compare the performance of multislice and single-slice electron ptychography on datasets simulated for crystalline PrScO₃, the same system used for our experimental measurements. For samples as thin as 8 nm, our simulation shows that multislice electron ptychography gains resolution improvement over the single-slice approximation. For thicker samples up to 30 nm, multislice electron ptychography demonstrates stronger performance improvements, showing the 59-pm separation of Pr–Pr dumbbells, whereas single-slice electron ptychography fails to capture even the basic structure. For even-thicker samples, such as those with 50-nm thickness, reconstructions are still possible, but higher
Multislice electron ptychography provides quantitative phase information, with the phase increasing linearly as more layers are added into the sample. Figure 1E shows the phase change at different atomic positions from reconstructions with different sample thicknesses. Such linearity is crucial for retrieving 3D structural information, especially for phase-contrast electron tomography, which requires a monotonic contrast dependence of sample thickness (24). Nevertheless, conventional methods such as scanning TEM (STEM) annular dark-field and annular bright-field imaging or high-resolution TEM (HRTEM) imaging always have a nonlinear or even non-monotonic dependence on thickness (figs. S3 and S4), and extensive simulations are required for quantitative image interpretation. Additionally, fast data acquisition and low-dose imaging capabilities that outperform conventional imaging techniques are retained in multislice ptychography, as in single-slice ptychography (figs. S10 and S11) (17).

We shift to experimental data collected on a 300-keV Titan Themis instrument with an electron microscope pixel array detector (EMPAD) (25). Full experimental details are given in the supplementary materials (23). Figure 2A shows one region of the phase image reconstructed by using an experimental dataset from a PrScO₃ sample with a thickness of 21 nm projected along the [001] zone axis, where the c axis of PrScO₃ is taken as the longest axis; this is the nonstandard Pbnm setting of space group 62 (a = 5.61 Å, b = 5.78 Å, and c = 8.03 Å) (26). The phase image resolves all atoms in the structure and outperforms state-of-the-art conventional electron microscopy (fig. S6) in terms of contrast and resolution: The heavy-metal atom sublattices for both Pr and Sc and the light-atom sublattice for O are resolved with a high contrast and signal-to-noise ratio. For these experimental data, both a partial coherence treatment of the electron probe (17, 27) and multiple slices (18, 21) are critical factors for obtaining a high-quality reconstruction (fig. S7).
The high–spatial resolution phase image of Fig. 2A is borne out by quantitative analysis. In real space, the Pr–Pr dumbbells with a separation of only 59 pm are resolved with a contrast of 63% (Fig. 2B), which is better than the 73% contrast for two point objects separated at the Rayleigh criterion. Therefore, the Rayleigh resolution of the image is much better than 59 pm. Nevertheless, the exact resolution can be determined only after considering the finite atomic size instead of assuming point objects (28). We can also resolve the O–Sc–O triple atom projections, even though the light O atoms are only 63 pm (26) from the heavier Sc atoms (Fig. 2C), and these cannot be resolved with conventional imaging techniques. The power spectrum from the Fourier transformation of the phase image (Fig. 2, D and E) shows an isotropic information transfer that is larger than 4.39 Å⁻¹, corresponding to 23 pm in real space.

To estimate the spatial resolution of the ptychographic reconstruction, the intrinsic width of the atoms needs to be taken into account. The static potential (Fig. 3D), each being roughly Gaussian in profile, can be added in quadrature and approximately modeled as a convolution of one Gaussian function with the static, frozen potential (Fig. 3C). The combined effects of limited resolution and thermal fluctuations on the measured potential (Fig. 3D), each being roughly Gaussian in profile, can be added in quadrature and approximately modeled as a convolution of one Gaussian function with the static, frozen potential (23). From the experimental data, the measured widths [full widths at half maximum (FWHMs)] of each atomic column estimated from more than 60 atomic columns are 44 ± 1 pm, 45 ± 1 pm, and 54 ± 2 pm from Pr, Sc, and O, respectively. By comparing the measured column widths with the Gaussian convolved potential, we can obtain the combined broadening factors (i.e., the FWHMs of the convolved Gaussian) of 28,
from experimental measurements of PrScO$_3$. The sample thickness is initially assumed as 30 nm during the reconstruction, but the retrieved sample thickness is 21 nm. The remaining residual broadening can be attributed primarily to the uncertainty imposed by the thermal vibrations in the sample. In other words, most of the measured broadening is already accounted for by the thermal vibrations in the sample. The remaining residual broadening can be attributed primarily to the uncertainty imposed by the finite incident dose and uncorrected instabilities (15). We estimate the residual instrumental contribution via quadratic subtraction, which gives the residual blurring (as a Gaussian FWHM) of our ptychographic reconstruction at Pr and Sc sites of 16 ± 1 pm and 15 ± 1 pm, respectively. Notably, QCBED produces a larger DWF for oxygen site #2 (O#2) than does XRD. The resolution of O#2 is 23 ± 2 pm or 19 ± 2 pm, depending on whether the QCBED or XRD result is adopted. It is not surprising that the resolution estimated from different elements is different, because the quality of the ptychographic reconstruction at a finite illuminated dose is dependent on the scattering power of the object (15). Therefore, the Abbe resolution of the ptychographic reconstruction, which approximately corresponds to the FWHM of the point-spread function (23), is better than 15 ± 1 pm, and its Rayleigh criteria, with a factor of 1.22 correspondence, is 18 ± 1 pm. In all cases, the column width of the ptychographic reconstruction is mainly limited by the finite size of atoms, as determined by their thermal fluctuations instead of the imaging system itself. Going forward, this method should be capable of measuring directional anisotropies of thermal vibrations for individual point-defect-like structures such as nitrogen-vacancy centers in diamond, which are being explored for applications in quantum computing and quantum communications.

In addition to the resolution improvement, the precision for measuring the atomic positions is also significantly improved. Figure 3E shows repeated measurements of Pr–Pr atomic distances with a standard deviation of 0.7 pm, which indicates that we have achieved a sub-picometer precision simultaneously with the 16-pm resolution. Notably, the positions of the light oxygen are also measured precisely. Because there are two different bond lengths in the distorted ScO$_6$ octahedra in PrScO$_3$, the Sc–O distances along two vertical directions,
labeled as $d_1$ and $d_2$ in Fig. 3D, are not equal. The precision is close to 1 pm, and the histogram in Fig. 3F shows $d_1$ and $d_2$ values of 203.0 ± 1.5 pm and 205.2 ± 1.3 pm, respectively. $d_1$ and $d_2$ differ by only ~2 pm, and picometer precision is required to distinguish such a small difference. However, high precision of atomic positions from conventional imaging techniques can be realized for heavy metals only (30); it cannot be achieved reliably for light elements such as oxygen (31). High precision of atomic positions and high-resolution measurement of both heavy and light atoms are crucial for correlating structure and function in materials. Multislice ptychography does not rely on lateral periodicity, so this technique can be applied to defects and grain boundaries as well as to single crystals.

Multislice electron ptychography also allows for 3D structure determination, because it iteratively retrieves the sample structure at different layers. The depth resolution and optimal depth sampling are determined by the out-of-plane curvature of the Ewald sphere and the largest scattering vector at which usable information can be collected (27). First, we check the reconstructed structures at different slices from the experimental results; three example slices are shown in Fig. 4A (all slices depicted in movie S1). We find that the slices at the beginning and the end (movie S1) show very small phase shifts. In the middle slices, the phase images show strong contrast and clear structural features. Figure 4B illustrates a depth profile of the phase change cut along the Pr–O direction (marked by the dash-dotted line in Fig. 4A). This depth evolution is generated because the sample is close to a parallel-sided film and there are vacuum layers above and beneath the film (Fig. 4C). The electron beam changes shape as a function of depth into the sample, which is properly accounted for in the multislice electron ptychography algorithm, and as a result recovers a phase shift that is linearly proportional to the electrostatic potential of the sample at each different depth slice. The broadening of the depth profile from each surface of the rectangular slab is fitted by an error function (23) and gives a depth resolution of ~3.9 nm, estimated from the width of the error function fitted to the phase variation versus depth at Pr sites (Fig. 4D). This value is better than the aperture-limited depth resolution of 5.1 nm from conventional optical sectioning (23).

We also find, through simulations, that multislice electron ptychography can enable the detection and location of interstitials and single atomic dopants in all three dimensions. We constructed a structural model by introducing single dopants in a 15-nm-thick PrScO$_3$ crystalline matrix and generated diffraction data by using multislice simulations (23). Dopant atoms with different atomic numbers (Z) will exhibit different visibilities in multislice electron ptychography because their potentials vary in width and magnitude. Therefore, we introduced defect atoms with a range of scattering strengths, from heavy (Pr; Z = 59) to light (O; Z = 8) and placed them at both interstitial (Fig. 4, E and F) and substitutional (fig. S14) sites and at different depth positions. Figure 4E shows the reconstructed phase images from 3 of 30 slices (movie S2) from the two Pr dopants at depths that differ by 3 nm. The depth profile across the two single dopants (Fig. 4F) shows well-localized contrast in all three dimensions. The depth resolution estimated from the full width at 80% of the maximum (FW80M) at the dopant peak in the depth profile (Pr2 in Fig. 4G) is 0.9 nm. Depth profiles from single Pr, Sc, and O dopants (Fig. 4G) are similar and show FW80M in depths of 0.9, 1.6, and 2.0 nm, respectively. This also shows that the depth resolution depends on the scattering power of the dopant, which in turn depends on the atomic number, as noted for the lateral resolution discussed earlier. A strong contrast and good depth resolution are also retained for single substitutional dopants on the atomic columns (fig. S14). Notably, the depth resolution from multislice electron ptychography exceeds the aperture-limited resolution ($\lambda/\alpha$, where $\lambda$ is the wavelength and $\alpha$ is the probe-forming semi-angle) and has an illumination-dose dependence (Fig. 4H). Additionally, the depth resolution depends on contrast and transverse resolution and can be potentially improved by collecting electrons scattered to higher angles and using a more converging or diverging electron beam (27).

Because conventional imaging methods are based on projections through the entire sample, single dopants embedded in a relatively thick matrix usually show little or no contrast (fig. S16). Only dopants with large atomic numbers in a light element matrix and a very thin sample may be detectable. For example, an Sb atom in a silicon matrix can be distinguished by STEM annular dark-field imaging (fig. S16). Only dopants with large atomic numbers (Z) where $\alpha$ is the aperture-limited depth resolution, from heavy (Pr; Z = 59) to light (O; Z = 8) and placed them at both interstitial (Fig. 4, E and F) and substitutional (fig. S14) sites and at different depth positions.
supervision of D.G.S., who also provided advice on XRD structural refinements; I.H. grew the PrScO₃ single crystal by the Czochralski method, under the supervision of S.G.; and Z.C. wrote the manuscript, with revisions from D.A.M. and input from all authors.

**Competing interests:** Cornell University has licensed the EMPAD hardware to Thermo Fisher Scientific. 

**Data and materials availability:** Raw experimental data of the results presented in the main text and supplementary materials are available from PARADIM, a National Science Foundation Materials Innovation Platform (34). The source code for multislice electron ptychography is available in the Zenodo repository (35).

**SUPPLEMENTARY MATERIALS**

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Materials and Methods

Figs. S1 to S17
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