

Mid-infrared wide-field nanoscopy

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Table of contents

- 1: Simulation of the heat diffusion from a 100-nm spherical object
- 2: Optical system of single-objective synthetic-aperture (SOSA) MIP-QPI
- 3: Pulse characterization
- 4: Reconstruction procedure of SOSA-MIP-QPI
- 5: Complete description of the SOSA-MIP-QPI reconstruction
- 6: Custom-made nanoscale spatial-resolution test chart
- 7: VIS-diffraction-limited MIP imaging
- 8: MIR spectroscopic analysis of bacterial intracellular structures
- 9: Principal component analysis of MIP spectroscopic images of the bacterium extracted from the commercial fermented soybeans
- 10: MIP images used for the statistical analysis of the three bacterial groups
- 11: Comparative analysis of the line profiles on the resolution test target
- 12: Simulation of the limit of spatial resolution of synthetic-aperture MIP-QPI
- 13: Simulation of MIP-QPI at sub-100-nm resolution

Supplementary Note 1: Simulation of the heat diffusion from a 100-nm spherical object

Figure S1 summarizes our heat-diffusion simulation that clarifies the importance of using a sub-nanosecond pulse for achieving VIS-diffraction-limited MIP-QPI. Details of the simulation are described in Methods.

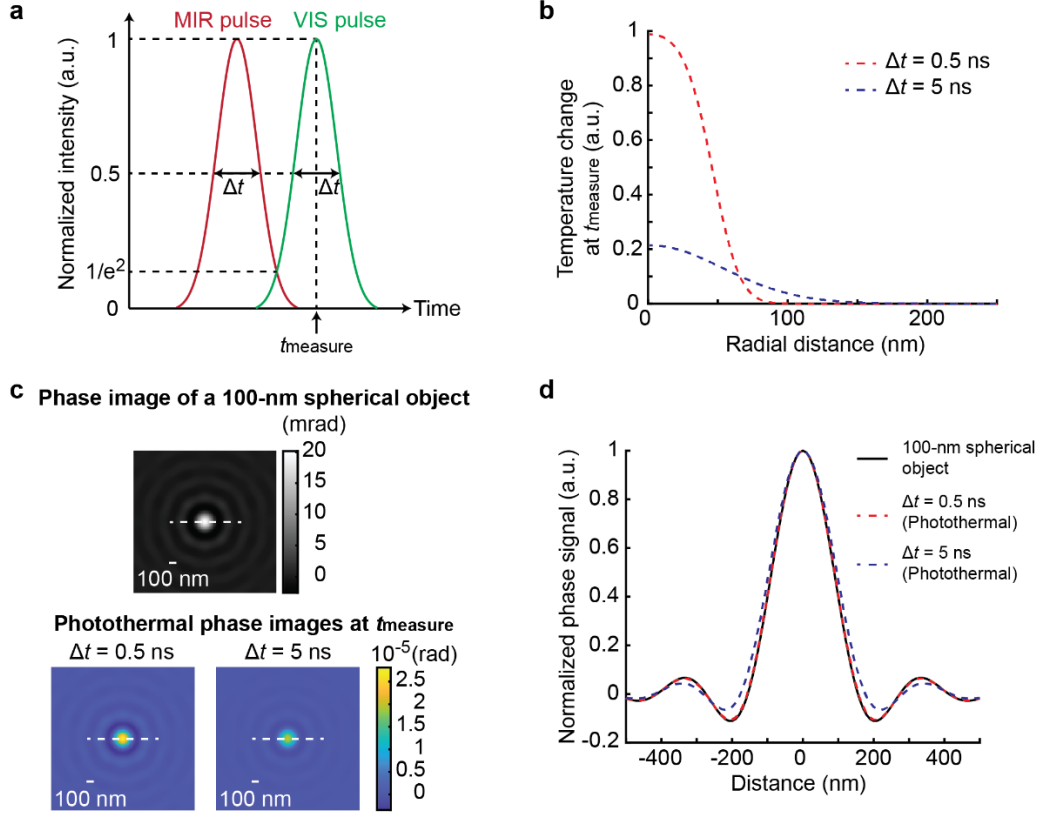


Figure S1: Simulation of the heat diffusion from a 100-nm spherical object. **a** Temporal intensity profiles of simulated Gaussian-shaped MIR and VIS pulses, where t_{measure} indicates the time when photothermal images are captured. **b** Radial distribution of temperature change at t_{measure} . The MIR pulse energy remains constant in the two cases with a pulse width of 0.5 or 5 ns. The maximum temperature rise for 0.5-ns heating is set to be 1 in an arbitrary unit. The results show that the temperature rise at the radial origin remains close to 1 with the 0.5-ns pulse, implying most of the induced heat has not diffused. Conversely, notable heat diffusion is seen with the 5-ns pulse. **c** Simulated synthetic-aperture OPD images of (top) the 100-nm spherical phase object and (bottom) the three-dimensional photothermal temperature-rise distribution at t_{measure} with the pulse width of (left) 0.5 or (right) 5 ns. **d** Normalized cross-sectional profiles of the images at the white dashed lines shown in **c**. The profiles reveal that the 0.5-ns pulse enables VIS-diffraction-limited photothermal imaging, while the 5-ns pulse does not.

Supplementary Note 2: Optical system of single-objective synthetic-aperture (SOSA) MIP-QPI

Figure S2 presents a complete schematic diagram of the optical system. The average input power into the MgO:PPLN crystals is 40 mW. The average power of the VIS pulses after the single-mode polarization-maintaining (PM) fiber is 0.65 mW.

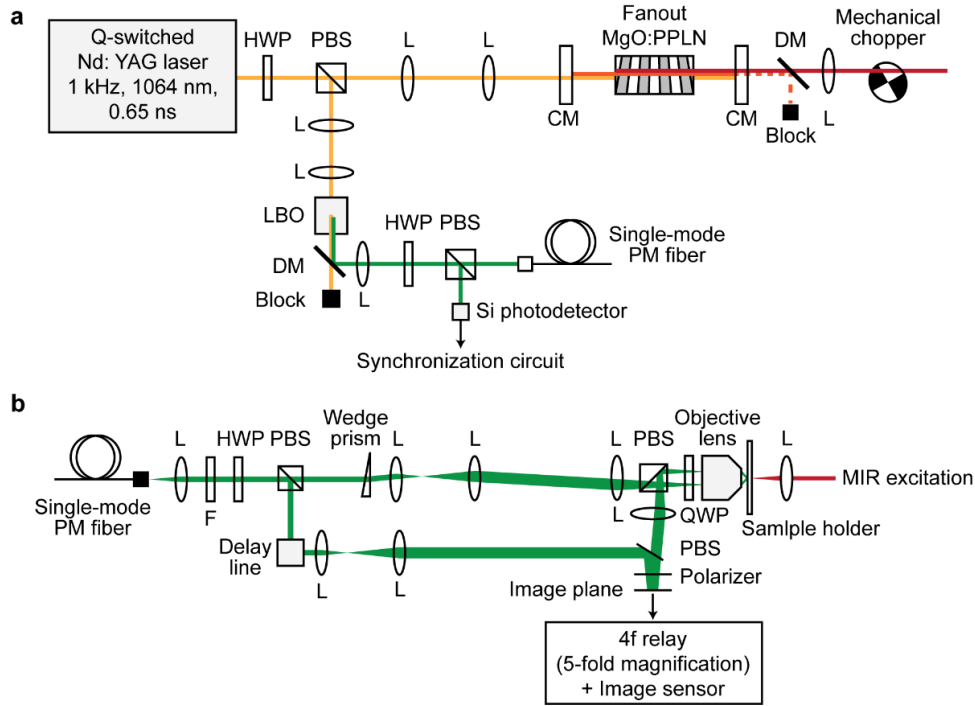


Figure S2. Complete schematic diagram of the optical system. a Passively-synchronized sub-ns laser system. **b** Single-objective synthetic-aperture (SOSA) MIP-QPI. HWP: half-wave plate, QWP: quarter-wave plate, PBS: polarizing beamsplitter, L: lens, F: bandpass filter (532 nm, FWHM 4 nm), CM: cavity mirror.

Supplementary Note 3: Pulse characterization

Figure S3a shows measured pulse durations of MIR, VIS, and seed laser pulses. Figure S3b shows spectra and pulse energies of MIR pulses at different wavenumbers. A 2-GHz Si photodetector was employed to characterize the temporal profiles of the VIS and the 1,064-nm pulses. Meanwhile, a quantum cascade detector (provided by Hamamatsu Photonics) was used to characterize the temporal profile of the MIR pulse. We used a home-made Fourier-transform infrared spectrometer to measure the spectral profile of the MIR light.

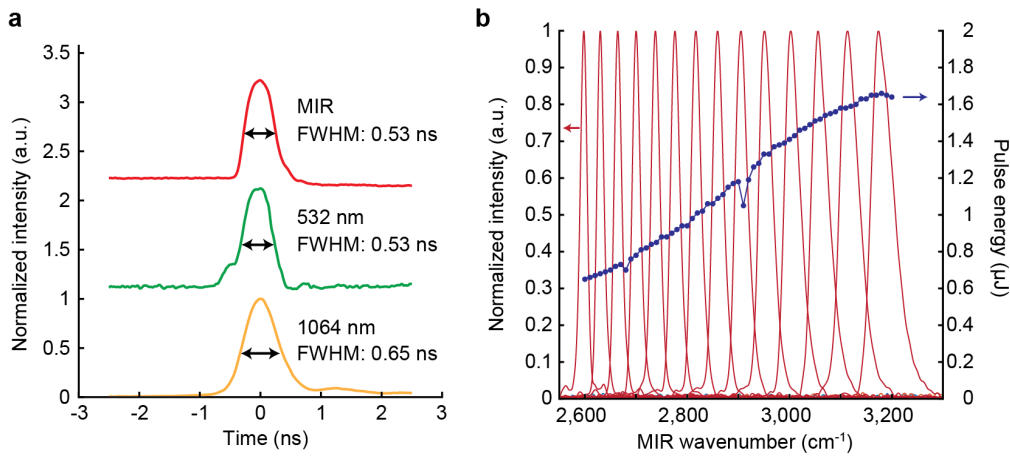


Figure S3. Pulse characterization. a Measured pulse durations of MIR, VIS, and seed laser pulses. **b** Spectra and pulse energies of MIR pulses at different wavenumbers.

Supplementary Note 4: Reconstruction procedure of SOSA-MIP-QPI

We describe the image-reconstruction procedure employed in our SOSA-MIP-QPI. In addition to the standard synthetic-aperture reconstruction algorithm, SOSA-MIP-QPI requires the computational removal of artifacts caused by MIR-photothermal alteration of the pupil function of the imaging system. Specifically, the MIR light is absorbed not only by the sample but also by the immersion medium between the objective lens and the sample, the cover glass, and/or the glass materials that constitute the objective lens. Such absorption changes the refractive index of these materials, altering the pupil function of the imaging system and thus causing artifacts in the photothermal image. Thanks to the computational nature of synthetic-aperture QPI, this effect can be computationally removed.

In Fig. S4, we use experimental data to explain this effect and the associated image-processing workflow. In this experiment, the custom-made spatial-resolution test chart is excited by MIR light with a wavenumber of 2,600 or 2,920 cm^{-1} . The latter wavenumber is resonant with C-H stretching modes in the organic resist, whereas the former is non-resonant.

Using Figs. S4a and S4b, we first explain how the pupil-function alteration induced by the MIR-photothermal effect appears in our raw data. Figure S4a shows an example where the pupil-function alteration is more dominant than the sample-specific MIR photothermal effect. It displays the OPD of the differential (i.e., MIR on-off) complex-field image (left panel) and its frequency spectrum (right panel) when 2,600- cm^{-1} MIR light, which is not resonant with the resolution test chart, is irradiated. A localized signal at the center of the circular pupil aperture in the spatial frequency spectrum is evident. This is uncharacteristic of the frequency spectrum of the resolution test chart, where noticeable signals are distributed along the horizontal and vertical directions due to the existence of vertical and horizontal bars, respectively, with various spacings in real space. Indeed, these observations are made with the frequency spectrum and the OPD image of our resolution test chart obtained with standard synthetic-aperture QPI, as shown in Fig. S4b. The non-sample-specific alteration of the pupil function in MIP imaging found in Fig. S4a appears as a non-negligible artifact in real space (left panel in Fig. S4a). Note that since the focused MIR light is irradiated to the sample at the normal incidence, this localized artifact of the pupil appears at its center.

Using Figs. S4c and S4d, we then explain how the effect of the pupil-function alteration is removed in the SOSA-MIP-QPI image-reconstruction procedure. We apply a high-pass filter to the circular pupil of the MIR on-off differential complex-field image so that the non-sample-specific alteration of the pupil is eliminated. The result of this high-pass filtering to the data shown in Fig. S4a is presented in Fig. S4c. In the left panel, we can observe that the non-negligible artifact appearing in real space has vanished due to the high-pass filter. Meanwhile, in the right panel, it is evident that some of the frequency contents are lost due to the high-pass filter. However, thanks to the aperture synthesis, the lost information can be filled with the measurements performed at other illumination angles. In an example shown in Figure S4d, the use of 8 azimuthal angles of illumination allows for filling the lost regions in the final synthetic aperture of the MIR on-off differential image. In the created synthetic spectrum, there is no evident signal with the non-resonant 2,600- cm^{-1} light turned on, whereas strong signal distribution in the horizontal and vertical directions, which is characteristic of the resolution test chart (Fig. S4a), can be observed with the resonant

2,920-cm⁻¹ light turned on.

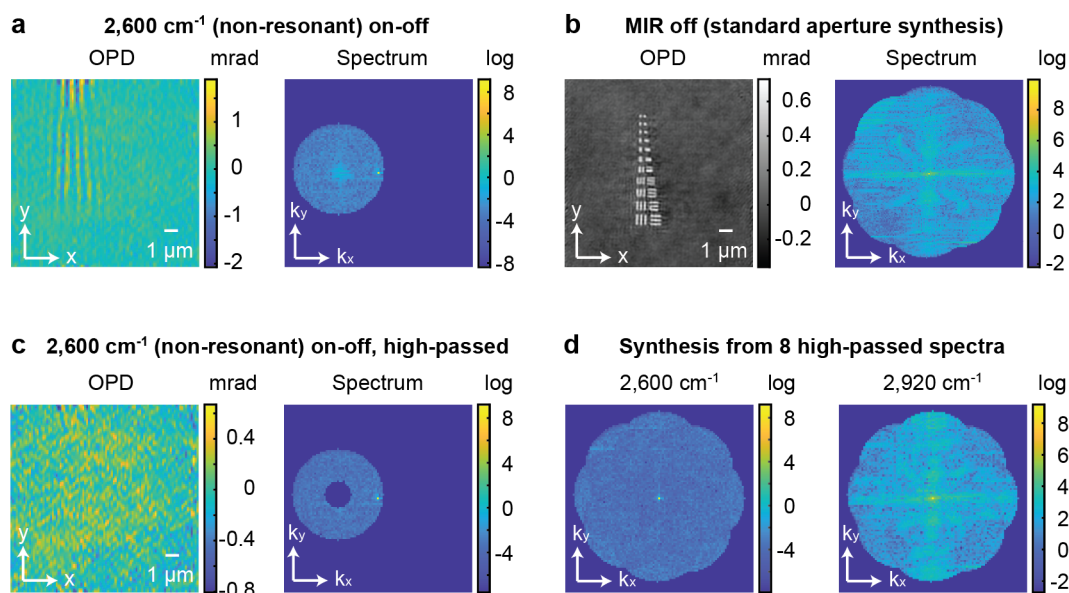


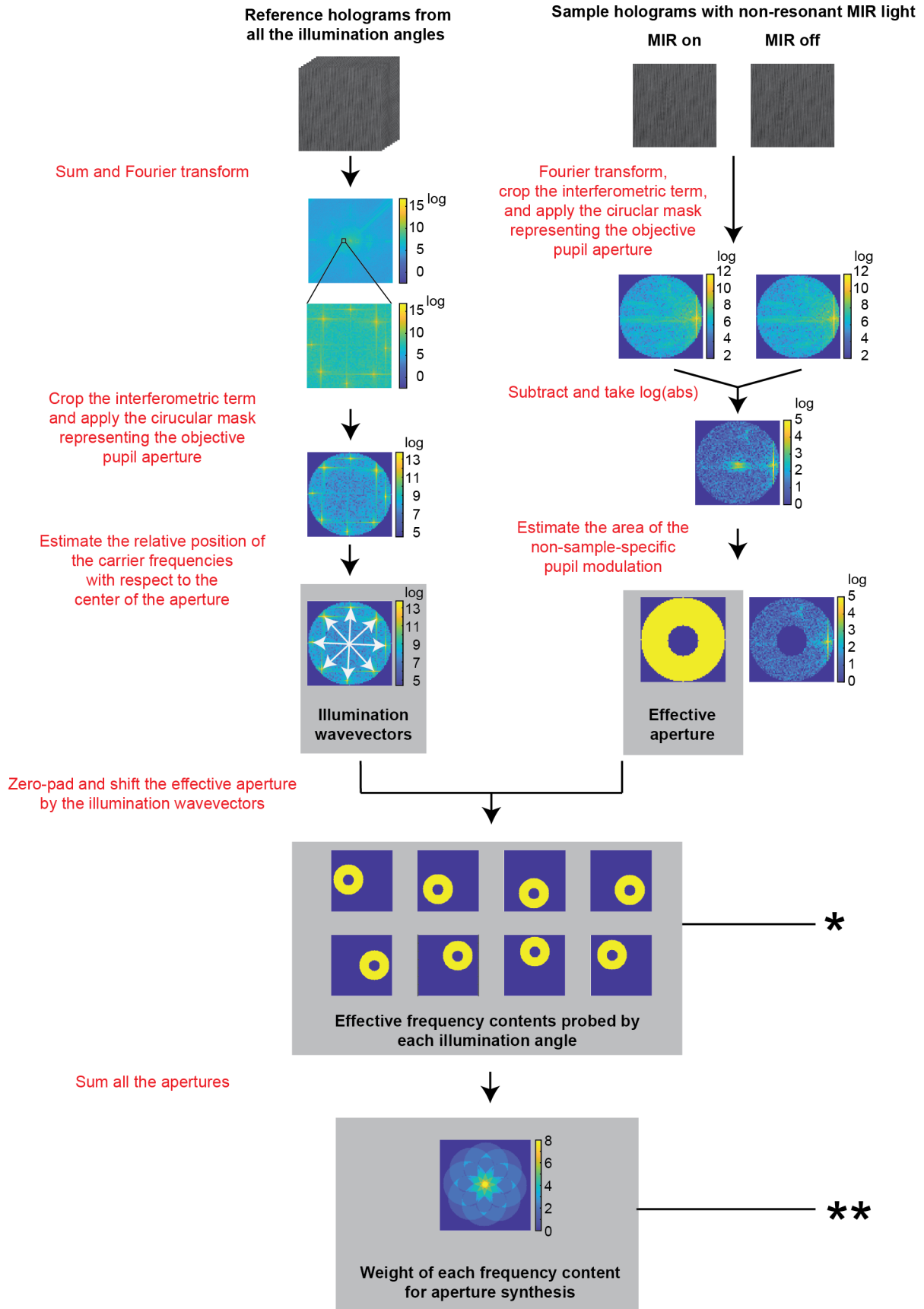
Figure S4. Reconstruction procedure of SOSA-MIP-QPI. **a** MIP image of the spatial-resolution test chart (left panel) and its frequency spectrum (right panel), obtained when the MIR light at 2,600 cm⁻¹ is irradiated. This wavenumber is not resonant with the vibrational modes included in the material of the test chart. A localized signal appears at the center of the circular pupil aperture in the spatial-frequency spectrum (right panel), which does not reflect the sample-specific signal distribution observed in the right panel of **b** and hence results in a non-negligible artifact in the real-space OPD image (left panel). **b** OPD image of the spatial resolution test chart (left panel) and its spatial frequency spectrum (right panel) obtained by standard aperture synthesis with the MIR light turned off. **c** Similar to **a**, but after the artifact appearing at the center of the circular pupil aperture has been removed through computational high-pass filtering (right panel). It results in the removal of the artifact in the real-space image (left panel). **d** Synthetic-aperture spectra obtained with 8 azimuthal angles of illumination. The central empty region of the computational aperture shown in the right panel of **c** is filled using these 8 azimuthal angles. When the non-resonant 2,600-cm⁻¹ MIR light is irradiated, there is no evident signal in the synthetic spectrum. In contrast, when the 2,920-cm⁻¹ MIR light, which is resonant with the C-H stretching modes included in the organic resist, is irradiated, strong sample-specific signals appear in the synthetic spectrum, showing similar horizontal and vertical distributions to those observed in the OPD image of the resolution test chart (right panel of **b**).

Supplementary Note 5: Complete description of the SOSA-MIP-QPI reconstruction

We provide a complete description of the SOSA-MIP-QPI reconstruction procedure in Fig. S5. An example dataset and Matlab code used for generating the images shown in the figure are provided at https://github.com/takuroideguchi/SOSA-MIP-QPI_2024_demo.

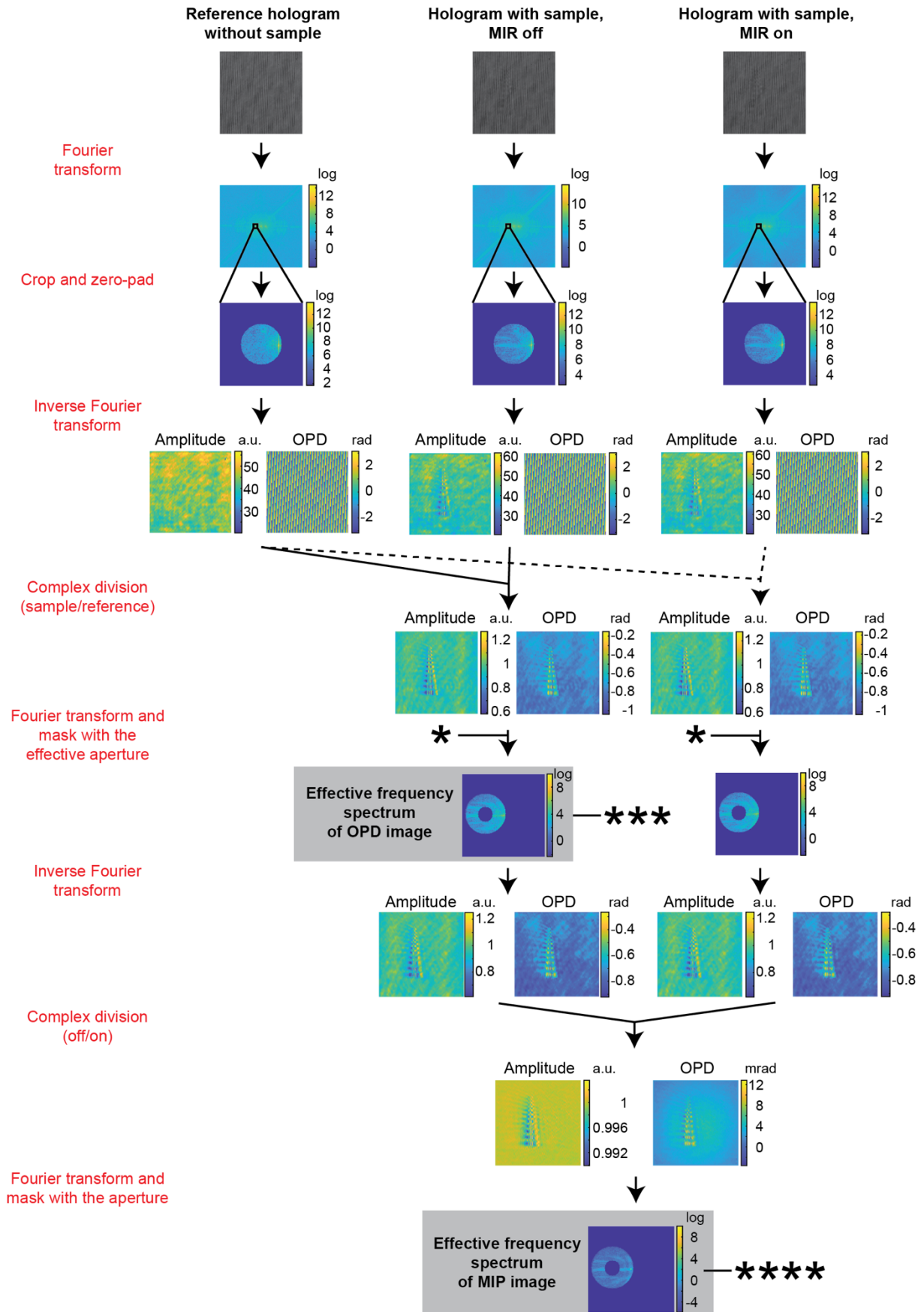
a

Step 1: Retrieval of the system parameters



b

Step 2: Reconstruction of the images at each illumination angle



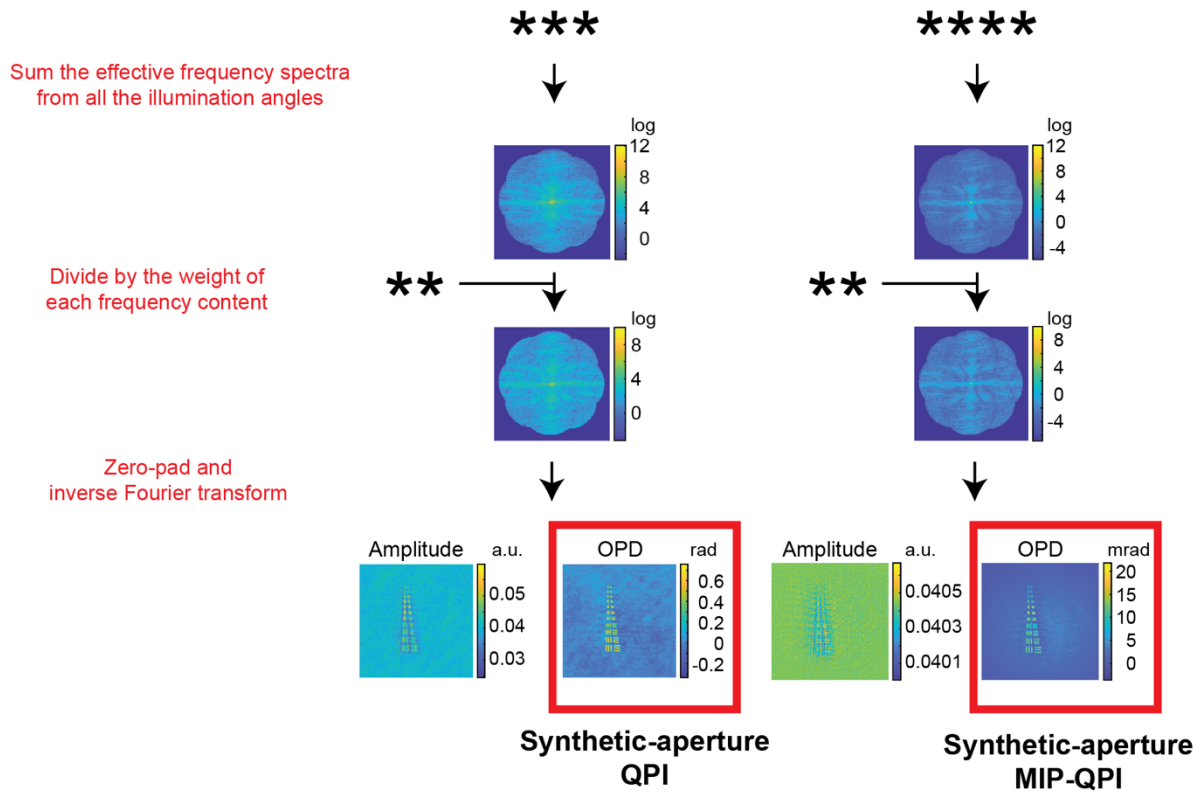
c**Step 3: Aperture synthesis**

Figure S5. Complete description of the SOSA-MIP-QPI reconstruction. **a** Step 1, where retrieval of the system parameters such as illumination wavevectors, effective aperture area, and weight of each spatial-frequency content for aperture synthesis is performed. **b** Step 2, where reconstruction of OPD and MIP images are performed for each illuminating wavevectors. **c** Step3, where aperture synthesis is performed.

Supplementary Note 6: Custom-made nanoscale spatial-resolution test chart

Figure S6 shows a scanning electron micrograph of the custom-made nanoscale spatial-resolution test chart. Several such charts were fabricated on the same silicon substrate. In the image, the 122-nm half-pitch bars are not spaced properly, but a chart that has well-spaced 122-nm half-pitch bars was selected for the experiments.

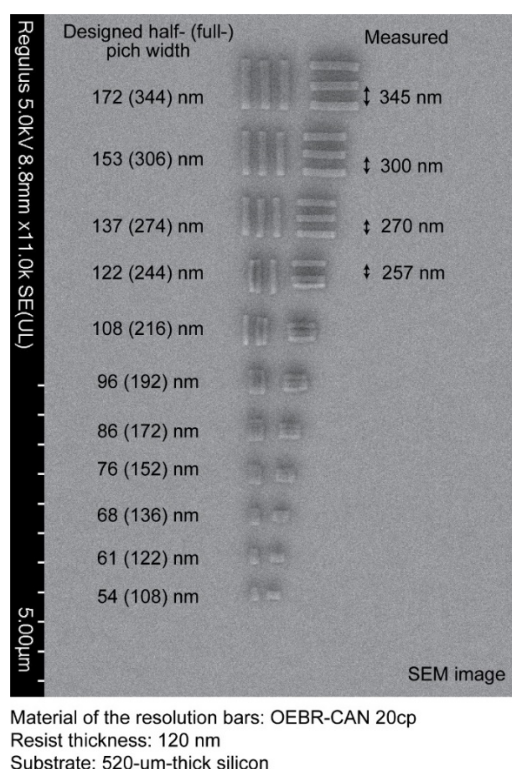


Figure S6. Scanning electron micrograph of the custom-made nanoscale spatial-resolution test chart.

Supplementary Note 7: VIS-diffraction-limited MIP imaging

We present our MIP imaging technique minimizes the effect of heat diffusion, realizing the spatial resolution determined by the VIS diffraction limit. To evaluate this, we fabricated a spatial-resolution test chart consisting of various sizes of nanometer-scale bars made from an organic resist deposited on a 520 µm-thick silicon substrate. Scanning electron microscopy confirmed the presence of bars with width and edge-to-edge spacing in the range between 100 and 200 nm (see Supplementary Note 6 for details). For observation using the water-immersion objective lens, we added a few drops of water and a cover glass on top of the silicon substrate and the test chart.

Figure S7a displays the synthetic-aperture OPD image of the test chart without MIR light. Figure S7b presents the MIP image of the same field of view obtained with the MIR light turned on, with a peak wavenumber of $2,920\text{ cm}^{-1}$ corresponding to the CH_2 anti-symmetric stretching mode resonance. Deconvolution between these two images (Figs. S7a and S7b) generates the PSF of the MIP image relative to the OPD image, as shown in Fig. S7c. This PSF represents the extent of spatial resolution degradation in MIP imaging compared to synthetic-aperture QPI. In the absence of spatial resolution degradation, the 2D PSF becomes equivalent to the inverse Fourier transformation of the synthetic aperture filled with unity, as shown in Fig. S7d. Horizontal and vertical cross-sections of these experimental and ideal PSFs are presented in Fig. S7e, where no degradation is observed in the FWHMs compared with the theoretical curve. This indicates that the spatial-resolution degradation due to photothermal heat diffusion is sufficiently suppressed such that the MIP image provides the same spatial resolution as synthetic-aperture QPI.

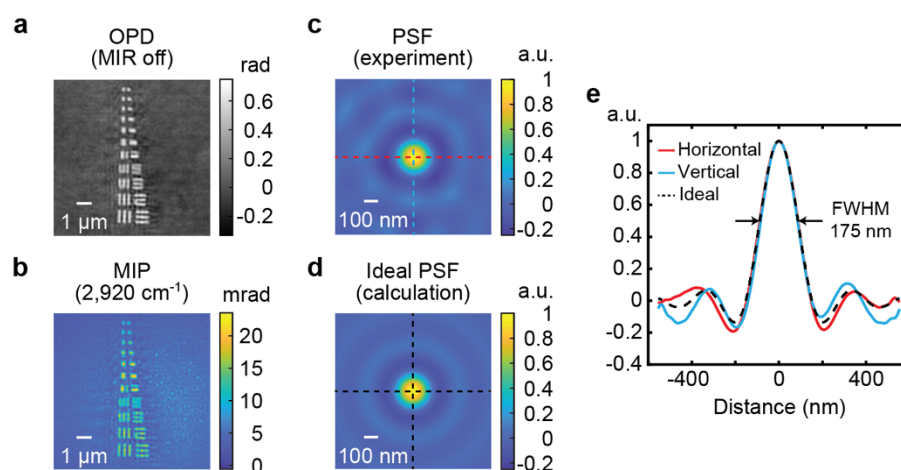


Figure S7. VIS-diffraction-limited MIP imaging. **a** Synthetic-aperture OPD image of the custom-made spatial-resolution test chart with the MIR light turned off. **b** MIP image of the same field of view, captured with the MIR light turned on, which peaks at $2,920\text{ cm}^{-1}$ resonant with the CH_2 anti-symmetric stretching modes. **c** Experimental PSF obtained by deconvolving the MIP image **b** by the OPD image **a**. **d** Ideal PSF calculated through inverse Fourier transformation of the synthetic aperture filled with unity. **e** Comparison of the cross-sectional profiles between the experimental and ideal PSFs. Dashed lines in **c** and **d** indicate the locations where the vertical and horizontal profiles of the PSFs shown in **e** are measured.

Supplementary Note 8: MIR spectroscopic analysis of bacterial intracellular structures

We present the biological applicability of our system by showcasing far-field MIR spectroscopic imaging of bacterial subcellular structures. We performed MIP spectroscopic imaging of a bacterium extracted from commercial fermented soybeans in the peak wavenumber range between $2,800$ and $3,500\text{ cm}^{-1}$, with an increment of 20 cm^{-1} . Figure S8a presents the OPD image of the bacterium. Through principal component analysis (PCA) of our raw spectral images, we identify several subcellular structures exhibiting unique MIR spectroscopic contrasts (see Supplementary Note 9 for details). Each of these structures is represented as a binary mask in Figs. S8b-d.

To perform MIR spectroscopic analysis of these subcellular structures, we display averaged and normalized MIP spectra obtained within these binary masks in Fig. S8e. For instance, in the circular structure represented by Fig. S8b, two sharp spectral peaks are observed at $\sim 2,860$ and $2,920\text{ cm}^{-1}$. These are likely attributed to the symmetric and anti-symmetric stretching modes of CH_2 functional groups, respectively, suggesting the presence of a lipid droplet. In the membrane-like structure presented in Fig. S8c, spectral peaks, characteristic of the symmetric and anti-symmetric stretching modes of CH_3 functional groups, appear at $\sim 2,860$ and $2,960\text{ cm}^{-1}$, respectively. Additionally, the spectrum exhibits broad peaks at $3,080$ and $3,280\text{ cm}^{-1}$, hypothesized to be amide B and A bands, respectively. Given the presence of the amide bands, the primary content of the membrane-like structure is assumed to be proteins and/or peptidoglycan. Furthermore, the spectrum shows a significant drop in the wavenumber region above $3,280\text{ cm}^{-1}$, which is characteristic of the amide A band. This suggests that the membrane-like structure contains minimal water. If water was present, it would not result in such a significant drop due to the O-H stretching mode, which exhibits a

spectral peak at $3,400\text{ cm}^{-1}$, as observed in the background spectrum. In contrast, the intracellular structure appears to contain more water, as its spectrum shows a shoulder at $3,280\text{ cm}^{-1}$, but not a significant drop at higher wavenumbers. This implies that the internal content of the bacterium is an aqueous protein solution. Importantly, these insights cannot be obtained from the morphology alone provided by the OPD image (Fig. S8a), highlighting the significance of MIP contrasts for label-free biochemical analysis.

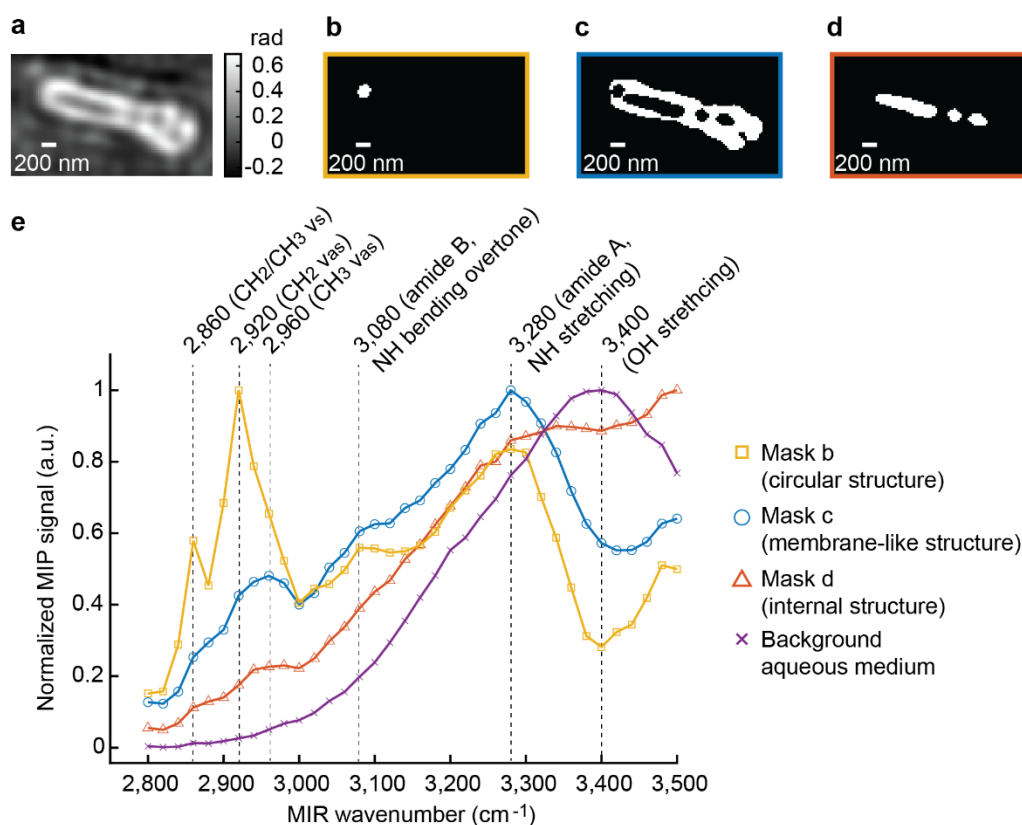


Figure S8. MIR spectroscopic imaging of bacterial subcellular structures. **a** OPD image of a bacterium extracted from commercial fermented soybeans. **b-d** Binary masks for distinguishing subcellular structures. **e** Averaged and normalized MIP spectra obtained within the binary masks shown in **b-d**.

Supplementary Note 9: Principal component analysis of MIP spectroscopic images of the bacterium extracted from the commercial fermented soybeans

Figure S9 shows the result of PCA performed on the MIP spectral image dataset presented in Fig. S8. The first three principal components (PCs) are found to represent noticeable bacterial subcellular structures. From this result, we estimated the three binary masks (Fig. S8b-d) that represented these subcellular structures and used them for a more detailed MIR spectroscopic analysis presented in Supplementary Note 8.

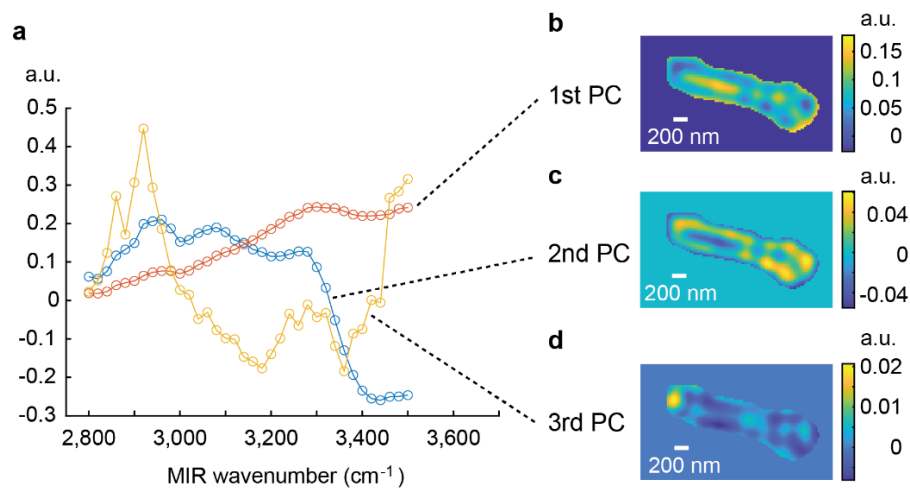


Figure S9. PCA of the MIP spectroscopic images of the bacterium extracted from the commercial fermented soybeans. **a** Coefficients of the first three PCs, representing unique MIR spectral signatures. **b-d** Score images of the first three PCs, representing unique subcellular structures.

Supplementary Note 10: MIP images used for the statistical analysis of the three bacterial groups

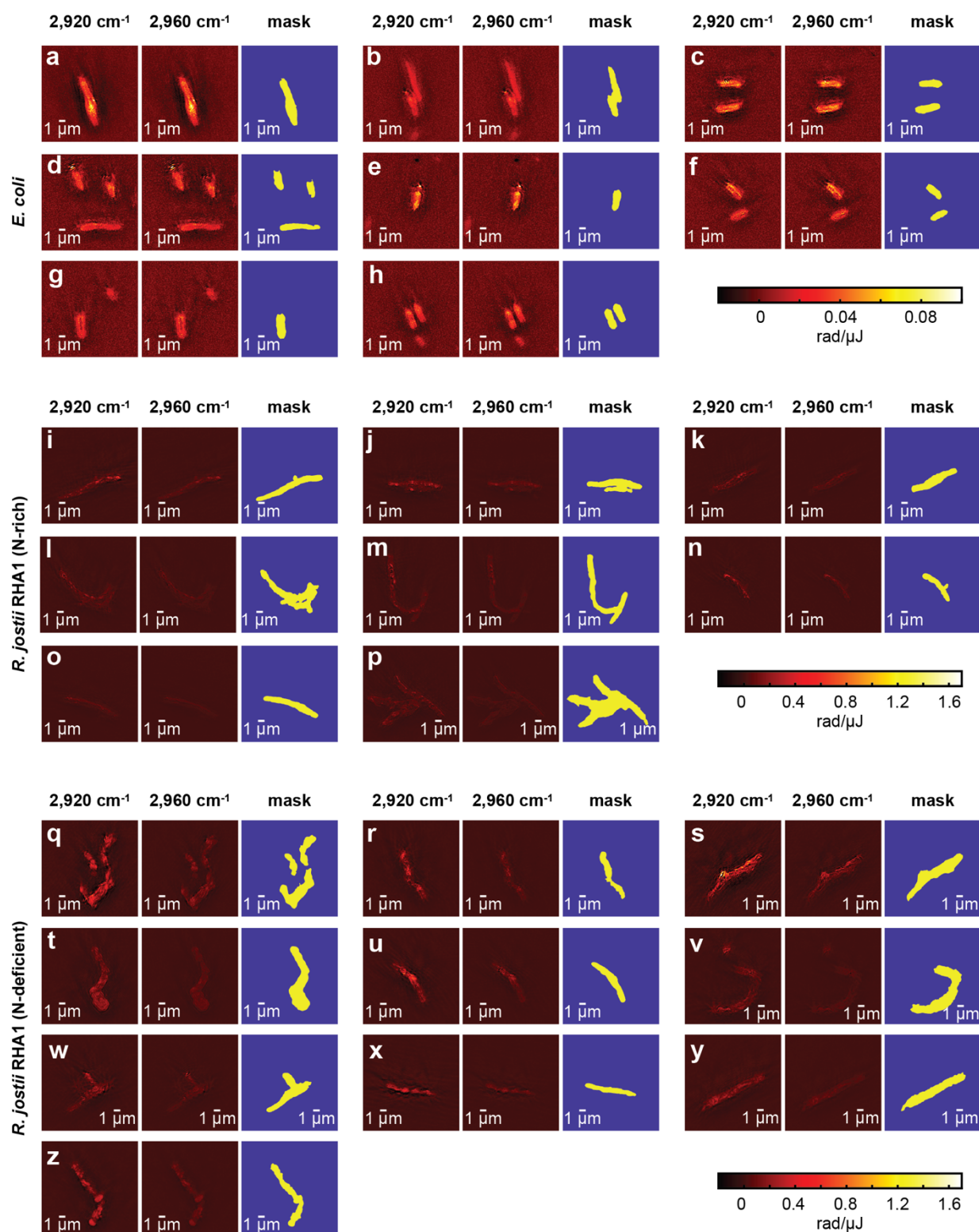


Figure S10. Normalized MIP images used for the statistical analysis of the three bacterial groups presented in Fig. 3 in the main manuscript. a-h *E. coli* cells. **i-p** *R. jostii* RHA1 cells cultured under the N-rich condition. **q-z** *R. jostii* RHA1 cells cultured under the N-deficient condition. In all the panels, the left and middle images represent the MIP images obtained with the MIR light tuned to 2,920 and 2,960 cm⁻¹, respectively. The right image in each panel

shows the binary mask used to segment the cellular regions in which the averaged MIP signals are calculated. The frame-averaging number for each azimuthal angle of illumination is **a** 600 (corresponding to 1,200 raw images), **b** 300 (corresponding to 600 raw images), **c-h** 200 (corresponding to 400 raw images), **i-p** 600 (corresponding to 1,200 raw images), and **q-z** 300 (corresponding to 600 raw images).

Supplementary Note 11: Comparative analysis of the line profiles on the resolution test target

We evaluate the performance of our experimental setup in terms of image contrast by comparing the images of the resolution test target obtained by our experimental setup and theoretical simulation.

To perform the simulation, we first measured the typical width of our fabricated resolution test target, which is below the diffraction limit of our SOSA-QPI setup, using scanning electron microscopy (Figures S11a and S11b). The images show that the width of the bars of interest, analyzed in Fig. 2 in our main manuscript and Fig. S7, is measured to be ~ 110 nm. We simulated an image of the resolution bars and their line profiles based on the measured width (110 nm) (Fig. S11c). We also simulated bars with widths of 20 and 150 nm and confirm that bar widths do not largely influence image contrast in this case. The vertical axis of the bottom graph showing cross-sections is the OPD value for the case of 110 nm. The profiles for the 20- and 150-nm widths are normalized to match the profile for the 110-nm width. The spacing of the bars can be clearly resolved and evaluated with our SOSA-QPI microscope because it is well above the diffraction limit. We first assess the magnification rate of our microscope as 333.9 ± 4.4 using the USAF test chart, as shown in Fig. S11g. Based on this magnification rate, the spacing of the bars shown in Figs. S11d-f, from center to center of the adjacent bars, is evaluated as 270 nm with an accuracy of ± 3.6 nm. The angular spectrum method was used to perform wave propagation using the experimental parameters: wavelength of 532 nm, illumination and collection NAs of 1.0 and 1.2, respectively. We used 8 azimuthal angles of illuminations with an increment of 45 degrees to perform aperture synthesis. The refractive index and thickness of the bars were set to 1.5 and 120 nm, respectively.

Figures S11d-f represent experimental images and line profiles of the resolution bars, which are compared with the simulation result. The comparison reveals that the experimental results show lower contrasts than the simulation. However, these lower contrasts are likely to represent the suboptimal performance of QPI rather than MIP imaging, which can be readily optimized by implementing existing computational techniques. The potential reasons for the lower contrasts are (1) the roughness of the coverslip contributing to non-uniform background OPD distribution and/or (2) the aberration of the imaging system. The effect of the first factor may be already mitigated in MIP imaging, because the differential imaging scheme does not require subtraction of a reference background OPD image that needs to be captured with the sample stage moved to an area where no object is seen. This may be why the contrasts of the MIP images shown in Figs. S11e and S11f are slightly higher than the contrast of the OPD image shown in Fig. S11d. On the other hand, the effect of the second factor is pervasive in any optical systems. However, it can be eliminated by a complex deconvolution technique¹ which is not difficult to achieve for any samples if a beam stirring mechanism is installed².

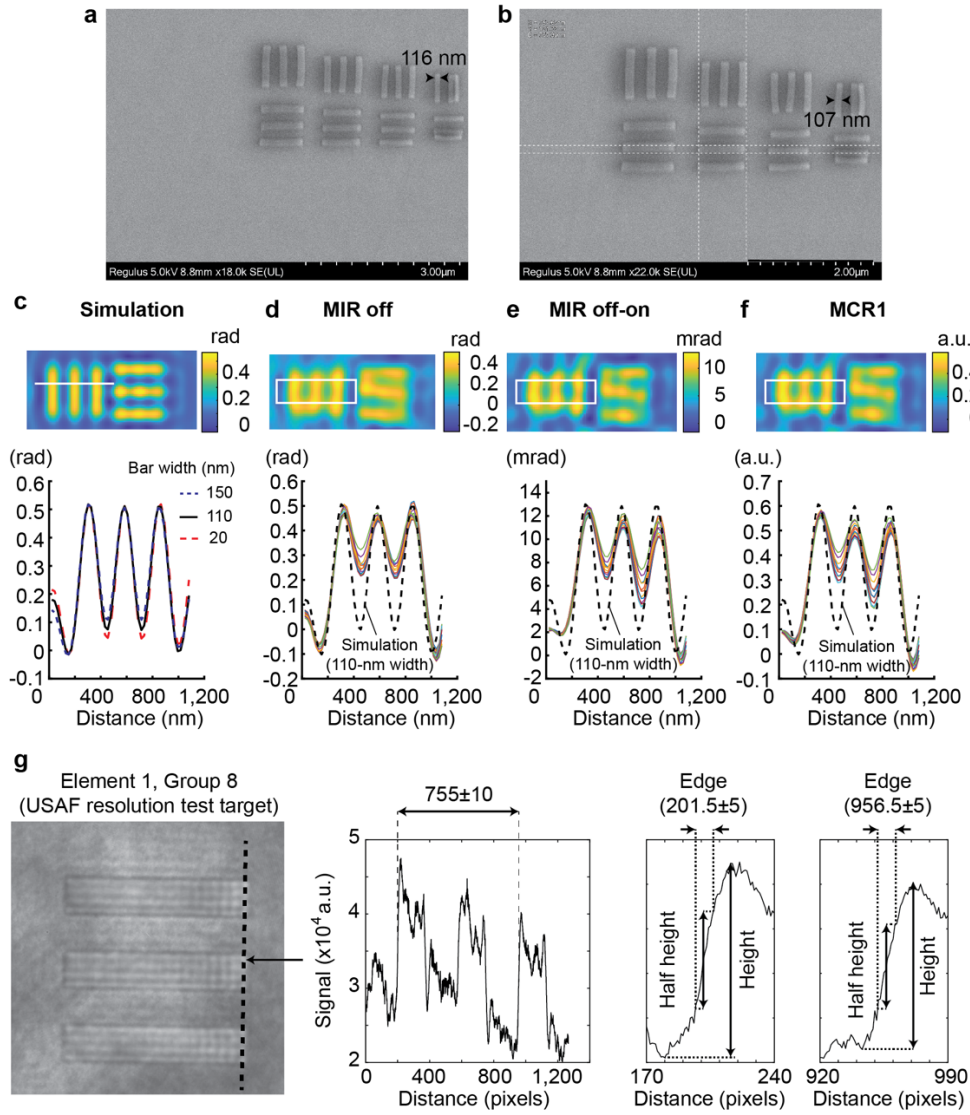


Figure S11. Comparative analysis of the line profiles on the resolution test target. **a, b** Scanning-electron micrographs of two different sets of the fabricated resolution test charts. **c** Simulated image of the resolution bars (top) and its line profiles (bottom) on the white line shown in the image. **d, f** Experimental images of the resolution bars (top) and their line profiles (bottom). The line profiles are measured at all the rows in the white-box areas shown in the images. **d** MIR-off OPD image shown in Fig. 2a in the main manuscript. **e** MIP image shown in Fig. 2a ($2,920 \text{ cm}^{-1}$). **f** “MCR1” image shown in Fig. 2c (inset). **g** Evaluation of the magnification rate of the experimental setup for calibrating the pixel resolution of the SOSA-MIP-QPI images. The width of the two line pairs of Element 1 in Group 8 of the USAF resolution test target (HIGHRES-2, positive, Newport) is measured as 755 ± 10 pixels. Since the pixel size of our image sensor (acA2440-75 μm , Basler) is $3.45 \mu\text{m}$ and the width of one line pair of this element is $3.9 \mu\text{m}$, the magnification rate of our microscope is evaluated to be 333.9 ± 4.4 , which agrees well with the designed value of 333.3. In this evaluation, uncertainty arises in the process of determining the edges of the line pairs, where the edge is assumed to fall within the pixels at which the signal value becomes (the midpoint of the edge) $\pm$ (a quarter of the height of the edge), as shown in the two right panels.

Supplementary Note 12: Simulation of the limit of spatial resolution of synthetic-aperture MIP-QPI

We performed simulations to derive the limit of spatial resolution with synthetic-aperture MIP-QPI. If the photothermal heat diffusion is sufficiently suppressed, the resolution limit is determined by synthetic-aperture QPI. To simulate this limit, We assume two-point scatterers, on a 1-nm-resolution 2D grid, with various spacings. The images are lowpass filtered with a synthetic aperture obtained with 8 azimuthal illumination angles with a 45-degree increment. In the first case that mimics our experimental system (i.e., with a wavelength of 532 nm and illumination and collection NAs of 1.0 and 1.2, respectively), the following resolutions are obtained: Nyquist-Shannon sampling resolution of 121 nm, FWHM of the imaged single scatterer of 175 nm (Fig. S12a), Sparrow limit of 189 nm (Fig. S12b), and Rayleigh limit of 211 nm (Fig. S12c). In the second case that assumes the optimized parameters (i.e., with a wavelength of 400 nm and illumination and collection NAs of 1.49), the following resolutions are obtained: Nyquist-Shannon sampling resolution of 67 nm, FWHM of the imaged single scatterer of 97 nm (Fig. S12d), Sparrow limit of 101 nm (Fig. S12e) and Rayleigh limit of 118 nm (Fig. S12f). Here, the Sparrow and Rayleigh limits of resolution are assumed to be the distance between the two scatters with which the contrast of the image (i.e., the dip in the cross-sectional profile) reaches 0% or ~25%.

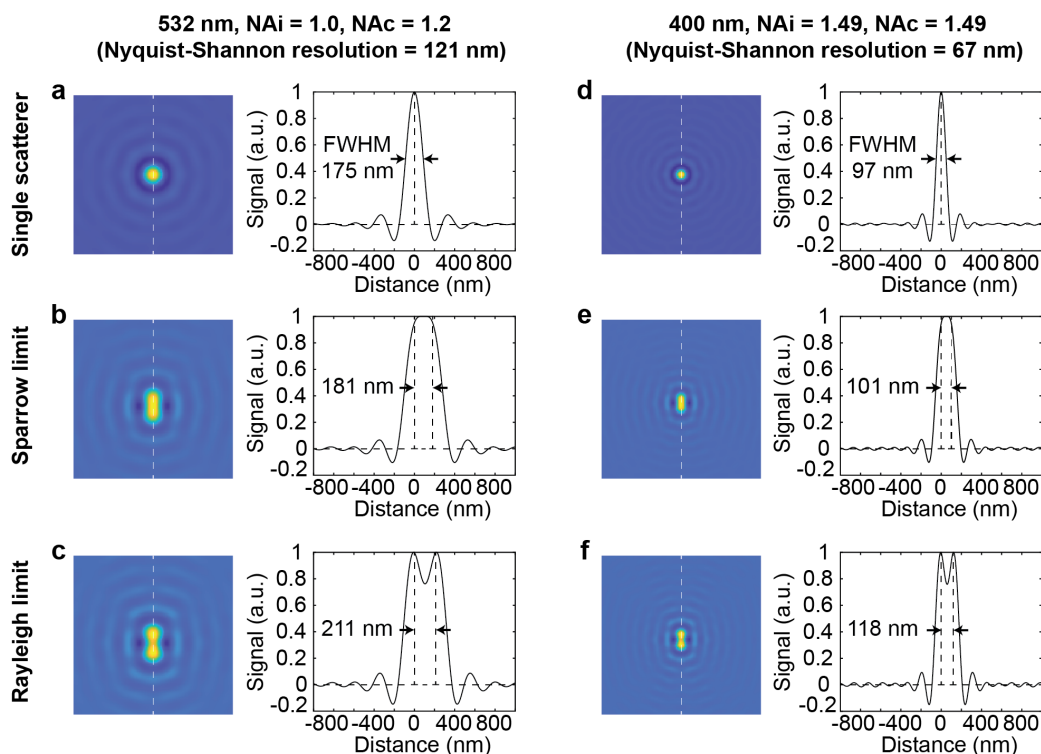


Figure S12. Simulation of the limit of spatial resolution of synthetic-aperture QPI. Each figure panel shows a simulated image of point scatters (left) and the cross-sectional profile (right) on the white dashed line in the image. The solid curves indicate the cross-sectional profiles of the images, whereas the dashed lines indicate the position of the point scatterers. **a-c** Simulations made assuming a wavelength of 532 nm and illumination and collection NAs of 1.0 and 1.2, respectively. **d-f** Simulations made assuming a wavelength of 400 nm and illumination and collection NAs of 1.49. **a, d** Simulation of the FWHM of a single scatterer. **b, e** Simulation of the Sparrow's limit of spatial resolution. **c, f** Simulation of the Rayleigh's limit of spatial resolution.

Supplementary Note 13: Simulation of MIP-QPI at sub-100-nm resolution

We performed simulations to show the potential of our SOSA-MIP-QPI method to achieve MIP imaging at a resolution of sub-100 nm. We simulated heat diffusion from a 20-nm spherical object by the same numerical method used in Supplementary Note 1 with the pulse widths of our current experimental implementation (i.e., 0.5 ns in FWHM). We used a wavelength of 400 nm, illumination and collection NAs of 1.49, and 8 azimuthal illumination angles with a 45-degree increment. Figure S13a shows the radial distribution of the simulated temperature rise normalized with respect to the radial origin. It can be seen that most of the induced heat is confined in the radial range below 50 nm, which is much below the diffraction-limited Nyquist-Shannon-sampling resolution of 67 nm derived in Supplementary Note 12. Figure S13b shows the simulated synthetic-aperture OPD image of the 3D temperature-rise distribution. Since the assumed object is much smaller than the illuminating wavelength, we integrate the 3D photothermal refractive-index-change distribution in the depth direction to estimate the 2D OPD distribution, which is then lowpass filtered by the synthetic aperture. The cross-sectional profile on the white dashed line in the image is shown in Fig. S13c. The profile reveals that the FWHM is measured to be 99 nm. This value is almost equivalent to the value obtained in the ideal case simulated in Fig. S12d, where no heat diffusion is assumed. Thus, the system yields almost visible-light-diffraction-limited spatial resolution characterized by the Nyquist-Shannon sampling resolution of 67 nm or FWHM of 99 nm.

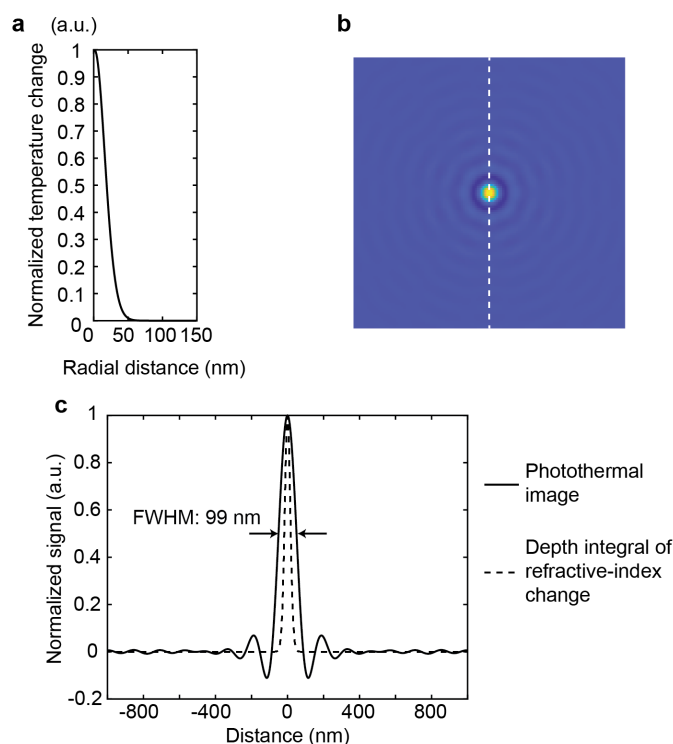


Figure S13. Simulation of MIP-QPI at a resolution of sub-100 nm. **a** Normalized radial distribution of temperature change caused by heat diffusion from a 20-nm spherical object. **b** Simulated synthetic-aperture OPD image of the 3D temperature-rise distribution. **c** Cross-sectional profile of the image on the white dashed line in **b**. The dashed curve represents the depth integral of refractive-index change.

References

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2. Baek, Y.S., Hugonnet, H. & Park., Y.K. Pupil-aberration calibration with controlled illumination for quantitative phase imaging. *Opt. Express* **29**, 22127-22135 (2021).