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Multi-aperture Fourier ptychographic microscopy

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Abstract: We present a novel microscopy concept, termed Multi-Aperture Fourier ptychographic microscopy (MA-FPM), to enable implementation of parallel detectors in microscopy to increase the space-bandwidth-time product. MA-FPM is a synthetic aperture technique: an array of objectives together with tilt-shift illumination are used to synthesize high-resolution, wide field-of-view images. Here, the phase is recovered using Fourier ptychography (FP) algorithms unlike conventional optical synthetic aperture techniques where holographic measurements are used. In this article we report a proof-of-concept experiment by translating a lens and a detector to positions according to the proposed design and demonstrate high-quality imaging performance despite using nine-fold fewer illumination angles compared to an equivalent FP setup. Calibration procedures and reconstruction algorithm were developed to address the challenges of multiple imaging systems.

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1. Introduction

Perhaps the most important advantage of the emerging technique of Fourier ptychography (FP) [1] is the ability to record gigapixel images with sub-micron resolution using low numerical-aperture (NA) optics. In particular, FP provides wide-field, high-resolution imaging without mechanical scanning. Instead, an extended spatial-frequency spectrum of the image is assembled in time-sequence [2] and computationally integrated into a single high-bandwidth complex spatial-frequency spectrum of the image from which a high-resolution complex image is calculated [3,4]; i.e., the optical phase of the sample is also reconstructed. The enhanced resolution is achieved through synthesis of a high-NA illumination source; the high-frequency cutoff may then be equivalent to that of a higher-NA objective, but the recording and reconstruction process provides the greater depth of field and field of view associated with the low-NA objective used to record the band-pass images. These numerous advantages are offset, however, by the reduced recording speed associated with time-sequential synthesis of the high-NA illumination; a factor that is exacerbated by the requirement for some redundancy in the sampling of overlapping spatial-frequency bands [5–7].

In conventional microscopy the objective acts as a low-pass filter and the higher diffraction orders, familiar from the Abbe theory of image formation, are lost, reducing both the resolution and bandwidth of acquired images [8]. In FP, the objective does not act as a low-pass filter, but instead as a bandpass filter – but nevertheless all spatial frequencies not transmitted by the objective are lost. Since several bandpass images with differing spatial-frequency content are recorded in FP, a large space-bandwidth product (SBP) [7,9] is achieved with the quid pro quo of increased recording time. We report here a novel concept of multi-aperture Fourier ptychographic microscopy (MA-FPM), in which multiple objectives, each forming an image on an independent detector array, capture this diffracted light and hence increase the space-bandwidth-time product (SBTP) [7,10] for image acquisition by a factor equal to the number of objectives used. We discuss and evaluate the performance gains made possible through implementation of this concept. For initial proof of principle experiments we evaluate a nine-camera configuration (by translating a single lens and detector to the positions corresponding

to these nine cameras) to demonstrate a nine-fold reduction in the number of LED illuminations required to form a high-resolution image.

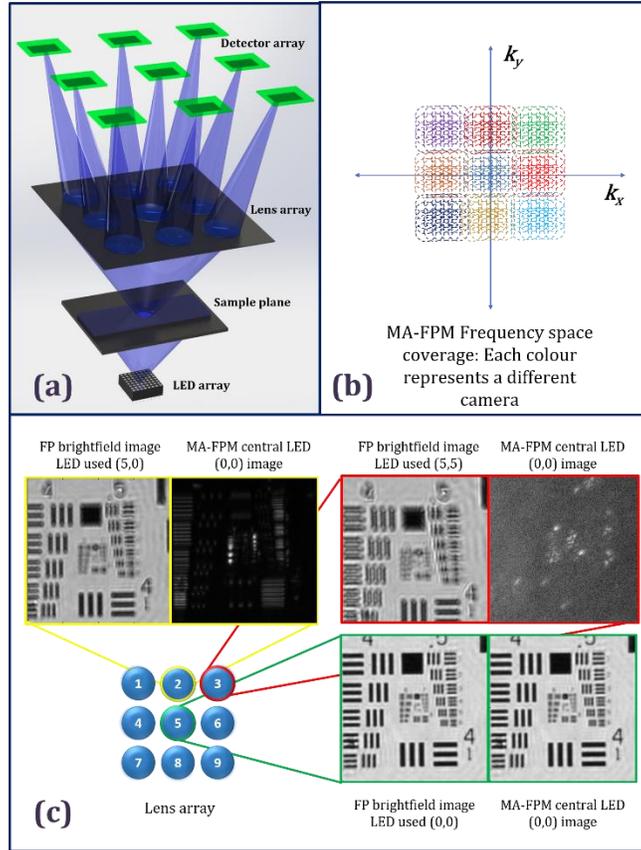


Fig. 1 (a) Planar MA-FPM setup. (b) Frequency space covered by each of the cameras. Each camera records a distinct set of spatial-frequencies for every LED illumination and covers a large section by combining all LED illuminations. This set is represented by a group of overlapping circles of same color. Each camera records such sets represented by different colors and these sets are unique to the camera. All the spatial-frequencies covered by these cameras contribute to the spatial-frequency content in the final image reconstruction. (c) Images obtained by the lenses in the array: Three lenses at different positions with various magnitudes of aberrations are chosen to demonstrate the differences in images and the spatial frequency content imaged. Images in the green box are from the central lens with zero off-axis aberrations, images in the yellow box are from a vertical lens which has off-axis aberrations in only one direction, images in red box are from a diagonal lens which has off-axis aberrations in both vertical and horizontal directions. In each set, images on the left are bright-field images where each lens requires different LED illumination to capture bright-field frequencies. Here it can be clearly seen that these bright-field images are mutually translated due to alignment errors and contain dissimilar aberrations associated with their off-axis positions. Images on the right are each obtained using the same central LED. Here each lens will record different set of spatial frequencies as observed.

The high-NA illumination in FP is implemented using an array of programmable light-emitting diodes (LEDs) [11,12] where each individual LED illuminates the object at a distinct angle, resulting in a shift of spatial frequencies sampled by the objective according to Ewald-sphere theory [13,14]. Band-limited images are stitched together in frequency space using alternate-projection type algorithms [15–17] to reconstruct the high-resolution optical field at the object. Since the complex field of the object is reconstructed, this technique can also provide dark-field and phase-contrast images of the object [18,19]. The image-reconstruction algorithms also facilitate estimation and correction of unknown aberrations in the optical system [4,20].

Fundamental to MA-FPM is the recognition that multiple apertures can record different parts of object's diffraction field, corresponding to different spatial frequencies of the object, in parallel enabling coherent reconstruction of the high-bandwidth complex amplitudes of the diffracted fields [21]. Consequently, MA-FPM synthesizes a single larger synthetic aperture, a concept widely used in radio-frequency imaging employed in astronomy and remote sensing for high-resolution imaging [22]. A key distinction however is that for radio frequency aperture synthesis, the electromagnetic field is directly sampled and correlated in the pupil plane with single-mode receivers, whereas in MA-FPM the field is sampled in the pupil apertures focusing onto detector arrays. In both cases redundancy in sampling is required to yield efficient complex calibration and image reconstruction.

Optical aperture synthesis has previously been reported in microscopy [23–26] but requires the complexity and sensitivity of optical interferometry for phase recovery and is limited to a single imaging aperture due to experimental difficulties. Conversely, our use of FP-based iterative computational calculation of diffracted complex fields, sampled by multiple apertures, enables a flexible combination of time-sequential and snapshot imaging to yield both increased spatial resolution and reduced recording time. The experimental complexity required for conventional interferometric aperture synthesis can be considered to be exchanged for the increased computational complexity required to compute the final image. This modern approach to imaging exploits the exponential increase in the power of low-cost computing.

In MA-FPM, the increased space-bandwidth product recorded in a single snapshot enables a reduction in the number of frames and total data acquisition time. That is, by using an $n \times n$ array of objective lenses the number of LED-illuminations can be reduced by a factor of n^2 , providing also a factor n^2 reduction in acquisition time. A further factor-of-eight reduction in acquisition is possible (for the optimal 65% overlap of spatial frequencies) by employing coded, multiplexed LED illumination [10,27–29]. It is noteworthy that if dense sampling by multiple objectives is implemented, MA-FPM provides a route to snapshot operation using an optimized array of only nine LEDs.

The lens mounting structures of practical multi-objective arrays result in gaps between lens apertures with associated gaps in frequency coverage for each acquisition. Hence, it is necessary for the design of the objective array and the LED array combination to permit recording of all spatial-frequency bands and retain the redundancy required for FP reconstruction [5,12,30]. The MA-FPM configuration depicted in Fig. 1(a) achieves this by matching the LED array size with the gaps between the lenses. To implement MA-FPM in microscopy, the off-axis geometry associated with large object-space NA means that it is necessary to employ custom-mounted discrete objective lenses rather than off-the-shelf integrated cameras as has been reported for macroscopic multi-camera FP [31]. Due to variations in geometry and manufacturing tolerances, each lens-detector pair in MA-FPM exhibits distinct aberrations and magnification, which we calibrate independently for optimization of image quality. In these circumstances the Fraunhofer approximation for propagation of light fields, which is conventionally employed in FP, cannot be efficiently employed [21,32]. We have therefore developed and applied a new reconstruction procedure based on Fresnel propagation [20,33,34] that enables correction for camera-to-camera variations in magnification and aberrations yielding a higher-quality reconstruction.

Prior to Fourier ptychographic stitching of the spatial-frequency spectra of the multiple images into a single high-resolution spectrum, co-registration of all recorded images is necessary. These images are dissimilar due to geometrical distortions and imaging aberrations and, of course, due to the differing image characteristics of the different spatial-frequency bands recorded (for example dark-field and bright field images are very dissimilar due to the corresponding high-pass filter and low-pass filter functions), and so conventional image registration algorithms [35,36] are ineffective. Our calibration procedure, described below, solves these problems to yield a high-quality image with an overall space-bandwidth-time

product (SBTP, i.e., the product of the frame rate and the space-bandwidth product for a single acquisition) that is much greater than that of a single camera.

Multi-camera imaging systems are also attracting increasing interest in macroscopic imaging; for example, to super-resolve aliased images and to enable increased functionalities such as foveal imaging and multi-spectral imaging [37–42]. The essential motivation is to introduce and exploit diversity to increase the data bandwidth through parallelized image recording: in spatial sampling, in magnification and in spectral bandpass in the above examples. These earlier multi-camera techniques incoherently combine multiple images, and hence cannot be used to recover phase and are limited to macroscopic imaging. However, our introduction of multi-camera imaging to Fourier-ptychographic microscopy is a coherent, aperture-synthetic combination of the complex spatial-frequency spectra. Hence, this is the first-time multiple camera geometry has been proposed to provide a route to increase the SBTP (here we demonstrate an order-of-magnitude reduction in the LED illuminations required). Multiple cameras in microscopy have been demonstrated in the past to capture light-field information or spectral information but not to increase the SBTP.

2. MA-FPM setup and methods

A. MA-FPM setup

The proposed MA-FPM setup, as shown in Fig. 1(a), consists of a planar array of objectives forming an array of images of the object on a parallel planar array of detectors. The array of detectors can be translated axially in unison for focusing. As highlighted above, FP may employ a simple, low-NA objective lens instead of a sophisticated, high-cost high-NA objective [43,44] to provide a route to low-cost high-throughput gigapixel microscopy. Hence, our MA-FPM system consists of an array of simple lenses, each sampling a distinct angular range of the light diffracted by the object, to form band-limited images at an array of detectors as depicted in Fig. 1(a). The effective NA for imaging is $NA_{\text{eff}} = NA_{\text{obj}} + NA_{\text{ill}}$, where NA_{obj} is the synthesized multi-objective NA and NA_{ill} is the synthesized illumination NA. Resolution therefore increases with both the number of objectives and the number of LEDs. Equivalently, an increased frame rate for a given SBP can be achieved by increasing the number of objectives while reducing the number of LED illuminations; for example, the effective NA that is achievable using a conventional single-objective FP system with 15×15 LEDs can be achieved by either 9 cameras and 5×5 LEDs or 25 cameras and 3×3 LEDs. For these two equivalent examples, multi-aperture FP offers a 9-fold and 25-fold increase in SBTP respectively compared to conventional FP. It should be noted that the spatial separation of the objectives in the first case would be larger and combined with a larger number of LED illuminations to provide the required spatial-frequency range. The geometry of the MA-FPM is chosen such that there is a minimum of 50% overlap between the spatial-frequency bands sampled by adjacent LEDs [5,30].

In the case of implementing LED multiplexing, an LED array with a minimum of 5×5 LEDs is desired to provide the degree of irregularity required in the multiplexed patterns [27]. FP is generally conducted in air without the benefit of oil immersion; the theoretical maximum NA is therefore limited to $NA_{\text{eff}} < 1 + NA_{\text{obj}}$. For MA-FPM, the NA_{obj} can be increased to unity synthetically using multiple apertures enabling a larger NA_{eff} . MA-FPM therefore provides the unique advantage over conventional FP of being able to attain high NA_{eff} (e.g. approaching two) using low-NA objectives, while retaining the low-NA benefits of large field-of-view (FoV) and depth-of-field (DoF).

Fig. 1(c) shows images recorded by three of the nine MA-FPM cameras: each camera may record both bright-field and dark-field images depending on the LED used for illumination. The bright-field images (on the left of each box), recorded with the appropriate co-axial LEDs, are mutually translated due to relative misalignment and are subject to dissimilar optical aberrations. For example, images recorded using the top-right objective are subject to the highest levels of off-axis aberrations (principally coma and astigmatism), while images recorded using the central and on-axis objectives are subject to much lower aberrations.

Conventional image-registration algorithms are therefore ineffective. For illumination by only the central LED of the 5x5 LED array, only the central camera of the 3x3 lens array, located at position (2, 2), records a bright-field image, while the other eight cameras record dissimilar dark-field images. Three of these images are shown on the right of each box: the central objective records low spatial frequencies (the bright-field highlighted green) whereas the objective at (2, 1), and diagonal lens at (3, 1), record high-band, dark-field spatial frequencies.

B. Calibration procedure

High-quality, artefact-free image recovery requires calibration of the system characteristics, in particular the pupil function (aperture shape and aberrations) and LED positions [3]. Additional factors specific to MA-FPM are camera-to-camera image registration and magnification. Magnification can be easily calibrated by imaging an object of known dimensions, but the image registration represents a greater challenge.

The variation in quality of the bright-field images apparent in Fig. 1(c) precludes the use of conventional image-registration algorithms. In our approach, we record calibration data for each individual lens system employing LED illumination such that each camera records the same spatial frequency band and hence can be mutually registered. Conventional single-objective FP images, with $NA_{FP} = NA_{obj} + NA_{ill}$, are constructed from these datasets for each lens using the FP-reconstruction procedure described in [27]. These images differ only in the translation arising from the uncertainty in detector positioning. An appropriate translation matrix is calculated by minimizing the error of the difference of these images to mutually align the high-NA images. These images can be aligned with an accuracy better than that of the recorded images due to the higher pixel count of the constructed images.

The pupil function for each lens can be recovered during the FP reconstruction due to the redundancy present in the acquired data [4] and this enables mitigation of imaging aberrations. The redundancy in the MA-FPM data captured is less than FP data since fewer images are recorded for each lens, but we compensate for this by increasing the redundancy in the calibration data by use of a larger number of LED positions than are used in image reconstruction. To further enhance the speed and robustness of convergence of the pupil-estimation algorithm we provide an initial estimate of the aberrations using a ray-traced model implemented using *Zemax*®. This calibration of the pupil function yields high-quality reconstruction as can be seen from the results presented later in Fig. 2 below. Errors in the LED positions can also be corrected, if required, by the techniques used in [45,46] on the calibration datasets.

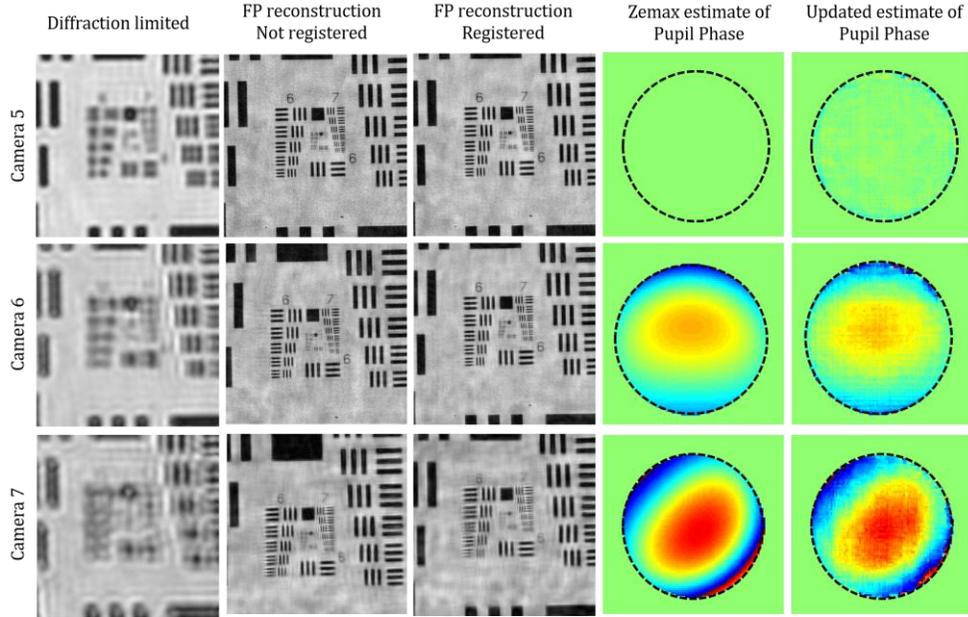


Fig. 2 Reconstructions of calibration data. The camera numbers correspond to the lens array schematic in Fig. 1(c). This image shows the center of the FoV. The colormap for phase reconstruction goes from $-\pi$ to π for all pupil phase images.

C. Reconstruction procedures

In a single camera FP system, the magnification and associated aberrations are identical for all recorded low-NA images. For a MA-FPM system however, aberrations and magnifications vary from camera to camera as described above, and the need for accurate correction will become more severe with increasing NA_{obj} and NA_{MA-FPM} , due to greater sensitivity to alignment errors. Stitching of images with dissimilar magnification using conventional FP algorithms requires image interpolation, which can in principle introduce additional noise into the images already suffering from aberrations and low SNR. Hence, we have developed an algorithm based on Fresnel propagation which enables stitching of images with dissimilar magnifications.

Data acquisition proceeds as follows. Each LED in the array is illuminated in time sequence and the cameras record a distinct spatial-frequency band specific to the LED position and the camera position. In this demonstration a single lens-detector system is scanned through a matrix of positions to simulate the array of objectives. The images from the array of camera positions are registered as described in the previous section and pupil functions for each of these lenses are obtained from the registration step. These registered images and the estimated pupil functions are used to calculate the synthetic image with a resolution associated with NA_{MA-FPM} using the reconstruction procedure described below.

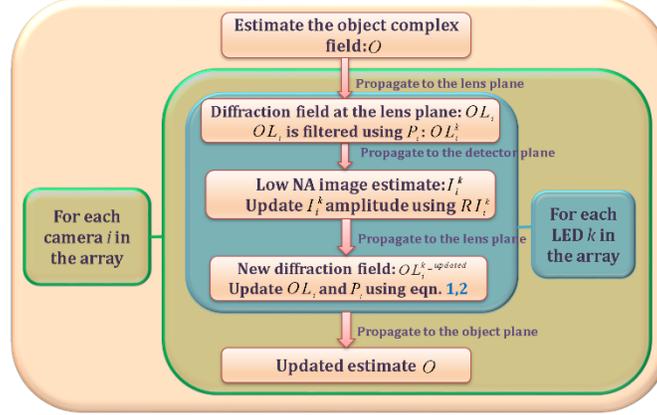


Fig. 3 Flowchart describing MA-FPM reconstruction algorithm. O is the high-resolution complex field of the object that is to be recovered, OL_i is the complex field due to the object in lens plane i , OL_i^k is the band-pass filtered complex field of the spatial-frequency band corresponding to the LED illumination angle k using lens i , P_i is the pupil function of the lens i , I_i^k is the estimated complex field on the detector plane for illumination by the LED at angle k using lens i , RI_i^k is the experimentally recorded intensity image for LED illumination k using lens i and $OL_i^{k, updated}$ is the updated complex field of OL_i^k .

MA-FPM reconstruction follows a process similar to FPM reconstruction procedures in [4,27] with a few generalizations to accommodate dissimilar pupil functions of the multiple camera positions and magnifications as summarized in the flowchart in Fig. 3. The reconstruction procedure commences by estimating the high-resolution complex optical field at the object, O , by interpolation of a low-NA image ($NA=NA_{obj}$). This object field has a factor eight more pixels than the corresponding image in each dimension in the detector plane (determined by the value of NA_{MA-FPM} [1]), and the size of each pixel in the object field is a factor $8M$ smaller than the pixel size on the detector plane, where M is the magnification of the system. The factor of 8 arises from the increase in the frequency bandwidth and hence pixel count achieved by FP. The complex fields OL_i at each lens plane is then calculated in sequence using the Fresnel approximation and taking into account the specific geometry for each lens as described in the appendix.

The complex field OL_i at each lens i is filtered using the pupil function, P_i of the lens, shifted according to the illumination by LED k to obtain the filtered complex field, OL_i^k at the output of the lens plane. Propagation of OL_i^k to the detector plane yields I_i^k ; an estimate of the image for illumination angle k . The amplitude of this estimated image is known from the recorded intensity image RI_i^k . Hence the amplitude of I_i^k is updated using this information and the phase is retained. This is now propagated back to the lens plane to obtain an updated estimate of the complex field $OL_i^{k, updated}$ which contains only those spatial frequencies corresponding to the k^{th} LED illumination angle. This spatial-frequency information in the $OL_i^{k, updated}$ is used to update the corresponding spatial-frequency band OL_i using the second-order Gauss-Newton method described in [3]:

$$OL_i^{updated} = OL_i + \frac{|P_i| \cdot [OL_i^{k, updated} - OL_i^k]}{|P_i|_{max} \cdot (|P_i|^2 + \alpha)}, \quad (1)$$

and the pupil function of the lens P_i is updated using

$$P_i^{updated} = P_i + \frac{|OL_i| \cdot [OL_i^{k, updated} - OL_i^k]}{|OL_i|_{max} \cdot (|OL_i|^2 + \beta)}, \quad (2)$$

where α and β are regularization constants.

As shown in Fig. 3, this process is repeated for all LEDs in the array for each lens i . The new complex field OL_i is then propagated back to the object plane to obtain an updated estimate of the high-resolution complex field O , which is used to calculate the diffracted field at the next lens and the whole process is repeated for the next lens. This process is repeated for all the lenses which completes one iteration of the reconstruction procedure. The whole process is iterated several times until the RMS error between two successive iterations falls below a required criterion; typically, convergence is achieved for between fifteen and forty iterations, depending on scene characteristics.

3. Experiment and Results

We demonstrate an experimental implementation of a planar MA-FPM system consisting of a 3×3 lens array with illumination provided by a 5×5 LED array. This provides equivalent resolution and space-bandwidth product to a conventional FP system with a 15×15 LED array, but with a nine-fold increase in data acquisition bandwidth. The objective lenses are simple achromats with focal lengths of 36mm and aperture diameters of 3mm (Edmund Optics #47-655) giving an NA of 0.025 and a magnification of 1.7. An LED array (Adafruit P4) with LEDs arranged on a 4-mm period matrix was placed 257mm from the object plane to yield an overlap of 61% in the spatial-frequency bands recorded using adjacent LEDs. This configuration provides either a synthetic $NA_{FP} = 0.119$ when using a 15×15 LED array or an equivalent $NA_{MA-FPM} = 0.119$ using a 5×5 LED array, representing a factor of four increase in the NA of the objectives. The center-to-center separation between the lenses in the array is 4.25mm such that when the fifth LED from the center illuminates the object, a bright-field image can be seen on the off-axis lens system. The detector used was an *Andor Zyla 5.5* (16-bit sCMOS with $6.5 \mu\text{m}$ pixel size.) For convenience, in this initial proof-of-concept experiment, MA-FPM images were recorded sequentially using a single lens and camera system translated through a rectangular array of positions simulating an MA-FPM system. Exposure times were 100 milliseconds for central camera images and 1000 milliseconds for rest of the cameras, and all images were normalized with respect to their exposure time. The central camera records all the bright-field images and the off-axis cameras record dark-field images, and since dark-field images have much less intensity than bright-field images, different exposures are used to improve the SNR, as is routinely done in FPM [1]. The reconstructed images presented below were recorded using the red LEDs of the LED array (center wavelength 623nm and full-width at half maximum of 17nm). For reconstruction, the 2048×2048 -pixel image on the detector is divided into sub-image segments of 256×256 pixels and processed independently to satisfy the partial-coherence requirements [21].

In Fig. we present results for our MA-FPM system and an equivalent conventional FP system, which show similar image quality, demonstrating the validity of the techniques used to construct the image. MA-FPM images reconstructed with and without calibration are presented, which are indicative of the importance of calibration in achieving high-quality images. Fig. . a1-a4 shows images of a USAF resolution chart that demonstrates increase in resolution with increasing NA. The low-resolution bright-field image recorded by a single objective in the center of the array is shown in a3. The finest resolvable detail is group 5 element 4, corresponding to diffraction-limited imaging with $NA_{obj} = 0.025$. In image a1, recovered using conventional FP employing 225 LEDs, group 7 elements 4 and 5 are clearly resolved indicating the expected $NA_{FP} = 0.119$. Image a2 is recovered using our MA-FPM technique and also resolves group 7 elements 4 and 5 and with an equivalent $NA_{MA-FPM} = 0.119$ to that achieved with conventional FP. These results confirm that MA-FPM reconstruction using the calibration procedure described above compares well to an equivalent FP system, while offering a nine-fold increase in data-acquisition bandwidth. Fig. (b1), 4(b2) presents a spoke target imaged using our MA-FPM system that demonstrates the omnidirectional resolution improvement.

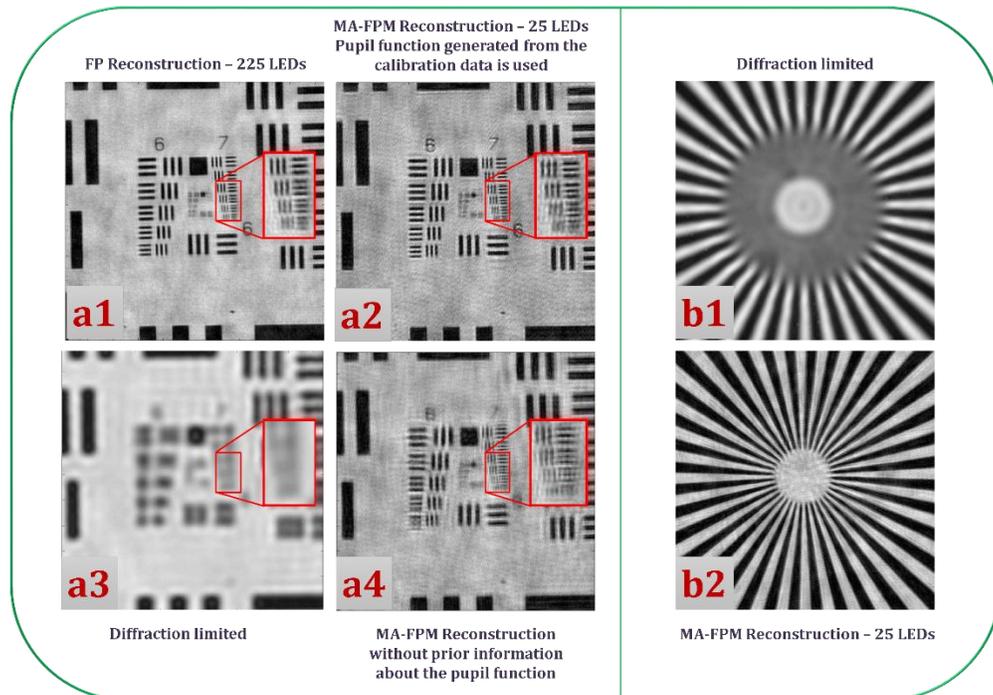


Fig. 4 MA-FPM validation results: (a1-a4) USAF resolution chart imaged to assess the resolution improvement quantitatively. a1– 225 LEDs FP reconstruction, a2 – 25 LEDs 9 cameras MA-FPM reconstruction using calibrated data and pupil phase estimated from calibration, a3 – diffraction limited image, a4 – MA-FPM reconstruction with calibrated data and without any pupil phase estimate (Most of the group 7 and some group 6 elements are not reconstructed properly). (b1-b2) A spoke target is imaged to show uniform improvement in the resolution in all directions, demonstrating that spatial frequencies in all directions are reconstructed.

Fig. (a4) demonstrates the importance of pre-calibrating the pupil aberrations. In this image, the reconstruction suffers from artefacts since the calibrated pupil phase estimate is not used in the reconstruction. In conventional FP, the pupil function is identical for all LED illuminations (225 in the case considered here) yielding a higher convergence rate than for MA-FPM (which uses fewer images per pupil: 25 in our example). An accurate initial estimate of pupil aberrations is therefore likely to be more important for MA-FPM than for FP. Our calibration allows us to achieve this by finding the best estimate of the system aberrations. MA-FPM reconstruction shown in Fig. 4(a2) has some minor enhancement in the noise from incorrect background subtraction [7] due to variations between the cameras. This is elevated in artificial test samples like USAF resolution chart but are not significant in natural scenes as can be appreciated by the images in Fig. 5. There is ongoing research to improve the background subtraction in FP, which can be extended to MA-FPM to correct for this if necessary.

A full-FoV reconstruction of an MA-FPM image is shown in Fig. : an image of a *Brunel* microscope slide of *woody dicotyled-stem cross section taken at 3 years*. It can be clearly seen that the recovered image exhibits very high resolution for the whole microscope slide. Three localized areas across the FoV are magnified to show the smallest features (cells of various sizes) that are recovered. These three image segments are taken from the central section of the FoV (highlighted in yellow), 30% of the FoV away from the center (shown in red) and 75% of the FoV from the center (shown in green) to demonstrate the high-quality reconstruction across a wide FoV. The reconstruction quality in the edges (over 75% FoV) is degraded slightly due to the higher levels of aberrations present in the edges of the FoV. These aberrations can be reduced experimentally using a Scheimpflug configuration for off-axis lenses [47]. We also

present the recovered phase of these segments on the right. The phase information recovered can be very useful to determine the structure of transparent samples without staining [10]. In the current sample the phase information can be useful to find the thickness and axial positioning of the cells.

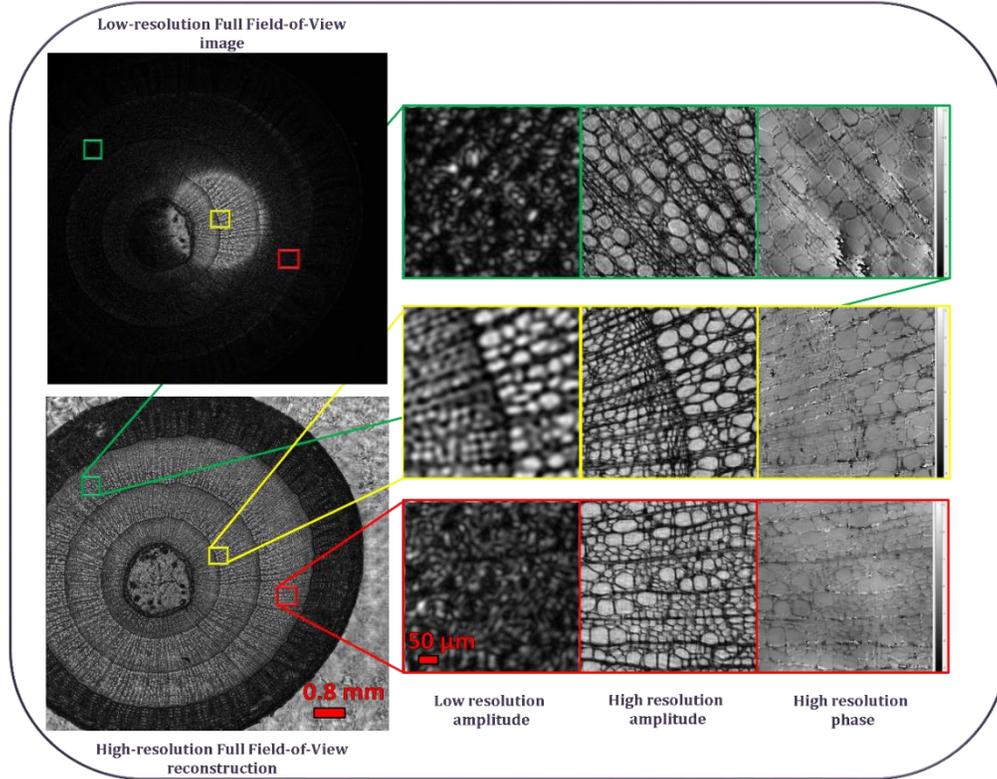


Fig. 5 Full FoV high-resolution reconstruction: *Brunel Woody dicotyled-stem cross section taken at 3 years* microscope slide imaged using MA-FPM. 3 different parts of the FoV are chosen to demonstrate the reconstruction quality across the FoV. Yellow box is the central section, red box is 30% of the FoV from center and green box is at 75% of the FoV from the center. In each box image on the left is the diffraction limited image, the central image shows the reconstructed high-resolution amplitude, and the right image is the reconstructed high-resolution phase. Colorbar for phase reconstruction goes from $-\pi$ to π for all three images.

4. Discussion

In the experimental design presented here, low-NA objectives (0.025NA) are used (rather than higher-NA objectives (0.1NA-0.3NA) as are commonly used in conventional FPM systems), since they provide the advantages of: wider FoV, extended depth-of-field and higher tolerance to alignment errors. In addition, a greater number of lower-NA objectives can be fitted within the desired synthetic-objective NA, as observed by comparing Figs. 6(a) and 6(b), to add more cameras for increased data throughput. The synthetic NA achieved by our system was limited to 0.125 due to the restricted travel of the translation stages used, however, our MA-FPM concept can be readily scaled to higher NAs (close to unity) by arranging the objectives on a spherical surface with the center of the sphere as the center of the FoV as shown in Fig. 6(c) and 6(e). The off-axis imaging systems in the planar array configuration suffer from aberrations as can be seen from the experimental results. These aberrations increase progressively with increasing synthetic NA of the system, and hence a curved array provides high-quality images with minimum aberrations, particularly when used in a Scheimpflug configuration [47]. A

higher synthetic NA can also be achieved with the current system by using more LEDs as shown in Fig. 6(d).

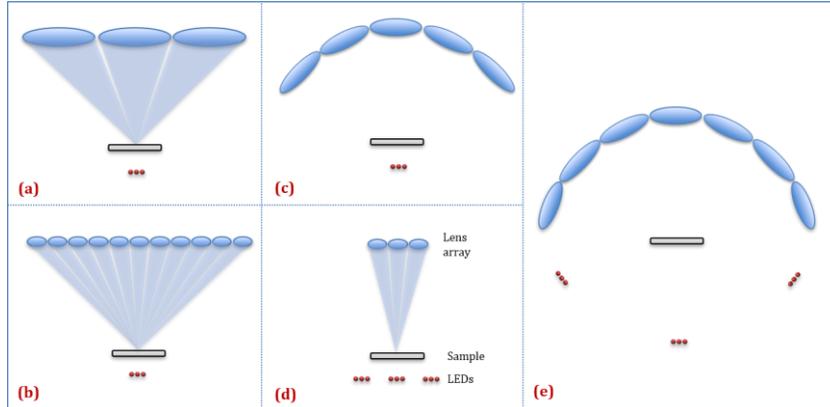


Fig. 6 Comparison of various possible MA-FPM configurations. (a) and (b) have similar synthetic NA but (a) has smaller FoV, hence smaller SBTP compared to (b). (c) To achieve high NAs a curved array system is preferred than a planar array to minimize the off-axis aberrations. (d) A high synthetic NA can also be achieved using lower-NA MA-FPM system by using a group of LEDs arranged for high-NA illumination as shown in the picture. (e) An MA-FPM configuration with synthetic NA close to two can be achieved by combining configurations (c) and (d).

A key challenge when using multiple cameras is the higher data-transfer rates. In this manuscript we have used one camera and captured the data in time-sequence, however, we are currently building a system with nine parallel cameras at higher NAs with higher data-transfer rate. Building such a data-transfer pipeline has previously been demonstrated several times in gigapixel photography [37], with up to one hundred cameras in parallel.

In a coherent microscope, the sample diffracts the light into a 2π hemisphere and using our proposed MA-FPM concept, several objectives can be fitted into this hemisphere (Fig. 6(e)) to collect this light in parallel, resulting in a NA 1 synthetic objective with wide FoV. This can be combined with NA 1 illumination LED array source, such as shown in Fig. 6(e), to generate a system whose synthetic NA can be close to 2. In microscopy, this is the only possible approach among the existing techniques to achieve close to 2 synthetic NA with high-speed data-acquisition using multiple detectors.

5. Conclusion

We have demonstrated a new aperture-synthetic MA-FPM microscopy concept that can theoretically achieve SBTP of many gigapixels per second and can be used to implement several imaging modalities. Our implementation uses a nine-camera design (simulated by translating a lens and a detector to these positions) to increase data acquisition bandwidth by a factor of nine compared to a conventional FP system. We report new image-reconstruction algorithms and high-quality image recovery in this new microscopy architecture, and calibration procedures to register images from multiple cameras with sub-pixel accuracies. The use of aberrations estimated from the calibration procedure enable faster convergence and improved reconstruction. The resultant images generated using MA-FPM are of comparable quality to a conventional FPM system but are obtained with a factor of 9 fewer sequential LED illuminations.

The proposed concept for parallel detectors implementation in MA-FPM offers a route to video-rate gigapixel microscopic imaging, which has not previously been possible. This is a primary requirement for imaging fast moving cell cultures [10]. MA-FPM retains all the advantages of conventional single-aperture FPM and can be very flexible in system design. For

example, sample-specific selective spatial-frequency sampling was proposed to reduce the number of LEDs used, which can also be implemented to reduce the number of cameras used [48,49]. Importantly, MA-FPM is compatible with schemes involving multiplexed-illumination to further reduce the data acquisition time, indeed it provides the possibility for snapshot imaging, with sub-micron resolution over fields of view measured in square centimeters. MA-FPM can also be easily adapted for various FP based imaging modalities [44,50,51]. Camera-array based imaging is becoming established in macroscopic photography and surveillance to improve the image resolution (for aliased imaging systems) and to acquire wide-FoV images, but this is the first time a camera array has been reported in microscopy to improve the spatial and temporal resolution of microscopes.

Appendix

Field propagation using Fresnel diffraction integral

In this section, we discuss implementation of the Fresnel diffraction integral to propagate the optical field between various planes in the reconstruction procedure. The sampling requirement in different planes is also discussed.

A. Diffraction integral with Fresnel approximation

The Fresnel diffraction integral that relates the field in the plane of interest (x, y) from a plane of origin (ξ, η) can be written in the form of a Fourier transform [1]:

$$U(x, y) = \frac{e^{jkz}}{j\lambda z} e^{j\frac{k}{2z}(x^2+y^2)} \iint_{-\infty}^{\infty} U(\xi, \eta) e^{j\frac{k}{2z}(\xi^2+\eta^2)} e^{-j\frac{2\pi}{\lambda z}(x\xi+y\eta)} d\xi d\eta, \quad (S1)$$

which can be rewritten in the form:

$$U(x, y) = e^{j\frac{k}{2z}(x^2+y^2)} \mathcal{F}\{U(\xi, \eta) e^{j\frac{k}{2z}(\xi^2+\eta^2)}\}, \quad (S2)$$

where the scalar factor is ignored for simplicity. Here multiplication of the complex field $U(\xi, \eta)$ with a quadratic phase factor accounts for near-field diffraction. This resultant field is then multiplied by another quadratic phase factor to give the propagated field in the plane $U(x, y)$.

Here the quadratic phase multiplied in both planes must be sampled according to the Nyquist frequency to avoid aliasing; i.e., we require that the sample period is such that [52]:

$$\delta < \frac{\lambda z}{2(\xi_{\max} + \eta_{\max})} \quad (S3)$$

where δ is the pixel period, λ is the wavelength, z is the separation between the planes, ξ_{\max} and η_{\max} are the maximum extensions of the complex field in transverse directions.

Propagation from the object plane to the lens plane

Denoting the complex field in the object plane as $O(x, y)$, the complex field in the lens plane, $L(\xi, \eta)$ is given by:

$$L(\xi, \eta) = e^{j\frac{k}{2u}(\xi^2+\eta^2)} \mathcal{F}\{O(x, y) e^{j\frac{k}{2u}(x^2+y^2)}\} \quad (S4)$$

where u is the propagation distance from the object plane to the lens plane, k is the wavenumber, (x, y) are coordinates in the object plane and (ξ, η) are coordinates in the lens plane.

Propagation from the lens plane to the detector plane

The complex field in the detector plane $D(\alpha, \beta)$ is given by

$$D(\alpha, \beta) = e^{j\frac{k}{2\nu}(\alpha^2 + \beta^2)} F\{L(\xi, \eta) e^{j\frac{k}{2\nu}(\xi^2 + \eta^2)} e^{j\frac{-k}{2f}(\xi^2 + \eta^2)}\} \quad (S5)$$

where ν is the propagation distance from the lens plane to the detector plane and f is the focal length of the lens. In this equation an additional quadratic phase factor is multiplied corresponding to the lens transfer function [34].

To propagate the field back from the detector plane to the lens plane and thence to the object plane similar equations to S5 and S4 can be used respectively, but with a complex-conjugate quadratic phase distribution. This would cancel out the requirement of multiplying the quadratic phase factor in the detector plane – relaxing the sampling requirement – since we are interested only in the amplitude distribution.

It should also be noted that in the lens plane three quadratic phase factors are multiplied before applying the Fast Fourier transform: (1) from propagating the field from the object plane to the lens plane from equation S4, (2) from the quadratic phase multiplied before propagating the field from the lens plane to the detector plane, and (3) from the lens transfer function as shown in equation S5. This quadratic phase is for an ideal lens without aberrations, but additional aberrations can also be incorporated. Multiplying these three quadratic phase factors will tend to cancel leaving the phase of only the aberrations. Hence the spatial sampling frequency is not a concern in the lens plane.

Nyquist sampling in the object plane requires careful consideration, however, from equation S3 it can be calculated that the sample interval in the object plane should be less than 10 microns, which is easily satisfied in our MA-FPM reconstruction since the pixel size in the object plane is around 0.2 microns.

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