

Structured illumination microscopy using extraordinary transmission through sub-wavelength hole-arrays

Margreet W. Docter,^a Peter M. van den Berg,^a Paul F.A. Alkemade,^b
Vladimir G. Kutchoukov,^a Oana M. Piciu,^c André Bossche,^c
Ian T. Young,^a and Yuval Garini^{a,d}

^a Imaging Science and Technology, ^b Kavli Institute of Nanoscience, ^c Micro-Electronics,
Delft University of Technology, Lorentzweg 1, 2628 CJ Delft, the Netherlands.

^d Physics Dept. & Inst. of Nanotechnology, Bar-Ilan University, Ramat Gan 52900, Israel.
m.w.docter@tudelft.nl

Abstract. A new microscopy method for multi diffraction-limited spot illumination is based on extraordinary light transmission through a periodic metal grid (typical period of 600 nm) of sub-wavelength holes (150 nm). Multiple spots illuminate a fluorescently labeled sample and the emission is collected by far-field optics. Theoretical comparison with a confocal microscope reveals equivalent spot sizes and a scanning method with the advantage of multiple illumination spots. The system is used to measure the actual transmitted field with a fluorescent sample in far-field. The obtained results are consistent with the theoretical prediction and provide a proof of concept of the midfield microscope.

Keywords: near field optics, extraordinary transmission, far field imaging, microscopy.

1 INTRODUCTION

Biological research and clinical diagnostics constantly require higher resolution microscopy methods. Confocal microscopy is currently the most common tool for high resolution three-dimensional (3D) imaging. It has a better optical resolution in the lateral direction than the wide-field microscope, but more importantly the out-of-focus blur is significantly reduced due to the appearance of the ‘missing cone’ in the optical transfer function (OTF). Yet, the image remains diffraction limited and the systems are rather complex because both the excitation and collection optics use pinholes which must be in conjugate focal planes. The acquisition time of a confocal microscope is rather limited due to the need to scan the object one point at a time. To speed up the acquisition, the confocal principle can be multiplexed, which has been done before by using a Nipkow disc [1-3].

Lately, another method of high resolution microscopy is developed called structured light illumination. In this method, a pattern is projected on the object and the resulting fluorescence is detected with a wide-field setup. In contrast to the confocal method mentioned above, this method does not use a pinhole or any other structures in front of the detector in the detection path [4]. It is advantageous with respect to confocal methods, due to the fact that a CCD can be used for the detection and the data can be processed to provide resolution improvement based on image processing [5]. In structured light illumination, the patterns of illumination are usually projected through a diffraction grating or through spatial light modulators [6]. It was shown that a significant improvement of spatial resolution beyond the diffraction limit can be achieved when processing the multiple illuminated images [7]. Structured light illumination was lately also combined with nonlinear effects of fluorescence, resulting in an even higher increase of spatial resolution [8].

We intend to use structured light illumination which is created by the direct transmission through a sub-wavelength hole-array instead of a diffraction grating or pinhole that is imaged

on the sample. The transmission through such hole-array is extraordinary because the presence of the holes allows coupling of light to surface waves, which contribute to the transmission for some parts of spectrum [9].

The microscope in which this extraordinary transmission is used is termed midfield microscope. It uses a near-field phenomenon for the illumination while the detection of the fluorescent emission is done in far-field onto a CCD. In order to predict the transmission pattern, 2D (slit-array) theoretical calculations are performed. Although the spectral peak is found for wavelengths λ larger than the array-period a , the transmission pattern for $\lambda < a$ is found to have a much better contrast and is more suitable for structured illumination. By using these calculations and the concept of the microscope, the theoretical point spread function and resolution are found, which are comparable to the confocal microscope if no frequency multiplexing is used. Super resolution can be obtained by using the structure of the light. Additionally to this theoretical concept, the transmission through the array is directly measured by observing fluorescent emission from a continuous solution. These results are comparable to the theoretical predictions and are actually a proof of concept. Such direct measurements of the transmitted field are presented here for the first time, to the best of our knowledge.

2 EXTRAORDINARY TRANSMISSION

Classically, it is expected that hardly any light passes a small (sub-wavelength) hole and if so, the light is totally diffracted. Bethe found the ratio of light passing a hole to be $(d/\lambda)^4$, depending on the diameter of the hole d and the wavelength λ [10]. However, if such a hole is periodically surrounded by other holes or grooves, more light passes a hole than impinges on it [9]. The transmission spectrum has peaks for certain wavelengths. A third characteristic is the narrow angular spread, which is measured to be 3° [11].

The cause of this extraordinary phenomenon is often subscribed to surface waves, in particular surface plasmons. The simplest prediction for a transmission spectrum is based on the existence of plasmons on a surface with a certain periodicity, and not taking the size of the holes into account [9]. Such a prediction is not accurate enough (around 10% off) and more advanced calculations are required. We use partial differential equations to predict the transmission intensity distribution which is often not shown in such calculations. We emphasize on the calculation of the intensity distribution, because it is crucial to the midfield microscopic method that we present, that we there will be high contrast of intensity in the transmission pattern. As will be shown, a high-contrast distribution is not necessarily related to a high peak in the transmitted spectrum, a fact that was not well discussed in prior works.

2.1 Calculated transmitted field

By using partial differential equations (implemented using the Matlab PDE toolbox [12]), the transmission of a plane wave incident perpendicularly on a gold film is calculated. Inside each medium (air and the gold film) Maxwell's equations are fulfilled (specified through the Helmholtz equations) and we adopt the Sommerfeld conditions stating that at the edges of the calculated area the waves are absorbed. It is possible to vary the thickness of the gold film (we used $t=200$ nm), the diameter of the slit ($d=150$ nm), the distance between the holes ($a=600$ nm) and the wavelength ($400 \text{ nm} < \lambda < 800 \text{ nm}$). We calculate the magnetic field H , from which the electric field E and the forward intensity flow, given by the z-component of the Poynting vector $P = \text{Re}\{E \times H^*\} / 2$, are derived.

Our calculations are limited to a 2D slit-array instead of a 3D hole-array, but similar results are expected for 3D. According to Altewischer [13] the polarization of light incident on a hole-array is decomposed along its principal axes, which implies that transmission through a 3D array can be seen as the sum of two orthogonal 2D arrays.

The spectrum is calculated by summing the forward energy flow at a distance of $1\text{ }\mu\text{m}$ from the array-exit. The most intense transmission is found for $\lambda > a$. However, the pattern found for $\lambda < a$ is much more interesting for use as structured illumination in our microscope. This pattern has a significantly higher contrast between the minimum and maximum intensity, and the spacing between the high intensity spots along the optical axis is more evenly distributed. In Fig. 1 both the spectrum and the transmission pattern are shown.

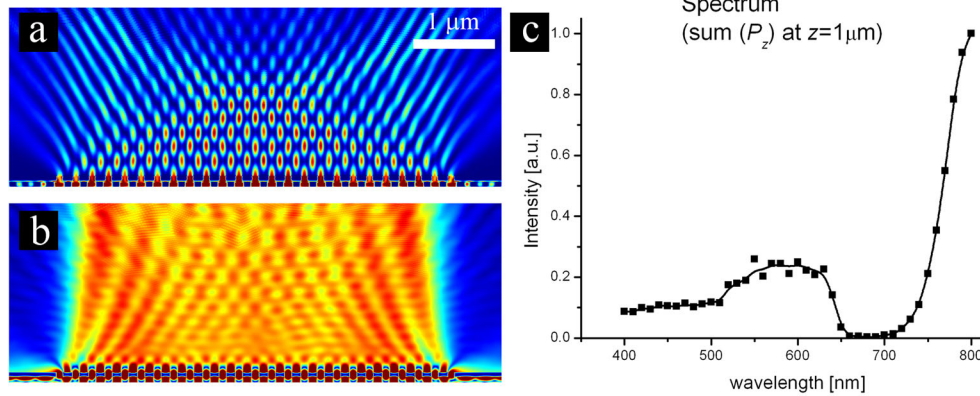


Fig. 1. Rigorously calculated transmission through a slit-array with 25 slits, $t=200\text{ nm}$, $d=150\text{ nm}$, $a=600\text{ nm}$ and $400\text{ nm} < \lambda < 800\text{ nm}$. White light impinges the array at the bottom of the image. (a) $\lambda=560\text{ nm}$, (b) $\lambda=800\text{ nm}$ and (c) the spectrum (all scaled to their maximal value).

The pattern in Fig. 1a resembles an interference pattern, which can occur because $\lambda < a$. The individual high intensity lobes are found to have dimensions that are similar to the illumination point spread function of the confocal microscope. Since the detection mechanism is also similar, the resulting point spread function (PSF) is comparable for both systems (see also section 3.1).

A similar pattern is observed by Shao [14], who used surface-plasmon-assisted nanolithography to observe the transmission pattern of a slit-array. The similarity of the measured pattern in [14] with our calculated field distribution strongly confirms the significance of the calculation.

3 MIDFIELD MICROSCOPE

A pattern with high distinct and high intensity spots is formed after light passing a golden array. This pattern has high potential to be used as illumination in the microscope we termed midfield. The image formation in this microscope is comparable with the confocal microscope in the sense that both of them use a limited illuminated area and detection through some sort of pinhole. After explaining the theoretical aspects on resolution, the experimental set-up and preliminary results are shown.

3.1 Resolution in midfield and confocal microscope

The resolution is defined as the shortest distance between two points that can still be resolved. This depends on the image of a single point, denoted as PSF_{system} . In the confocal microscope PSF_{system} is $(PSF_{lens})^2$ which is the result of multiplication of illumination and detection PSF_{lens} (with the appropriate illumination and detection wavelengths), both done with the same lens. In the midfield microscope the illumination is executed with the special transmission pattern through the hole-array. Therefore, the PSF_{system} is given by $PSF_{lens} \cdot TI$, in which TI is the transmitted intensity distribution.

The PSF_{system} , PSF_{lens} and TI are shown in Fig. 2. The full width at half maximum ($FWHM$) for the PSF_{lens} at $\lambda=561$ nm is 220 nm in focal plane and 590 nm along the optical axis. The size of the illumination spots of the midfield microscope depends on λ , a and d . For $\lambda=561$ nm, $a=600$ nm and $d=150$ nm a single illumination spot (TI) has a $FWHM$ of 220 nm in plane of focus and 490 nm along the optical axis. The PSF_{system} in plane of focus is the same for both and along the optical axis is only slightly narrower for the midfield than for the confocal microscope. The $FWHM$ of PSF_{system} is 160 by 400 nm for the midfield and 160 by 420 nm for the confocal microscope.

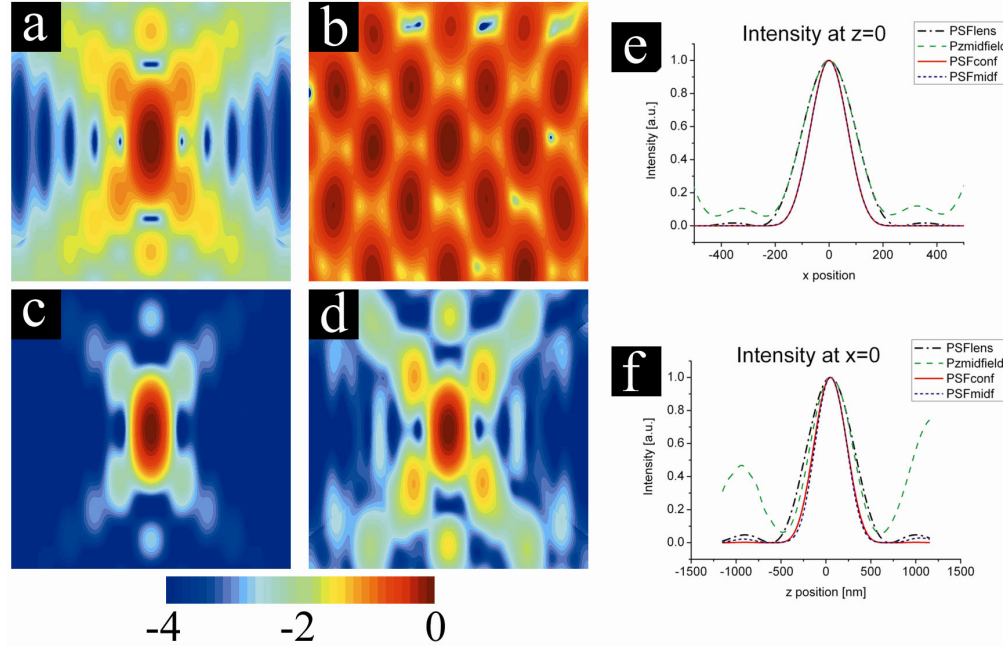


Fig. 2. The logarithmic values of (a) PSF_{lens} , (b) (part of) transmission through array (TI), PSF_{system} of (c) confocal and (d) midfield microscope, all calculated for $\lambda=456$ nm. (e), (f) linear line profiles along $z=0$ and $x=0$

Since the distance between the holes is 600 nm and $a > FWHM(PSF_{system})$, the images of each illumination spot are isolated from each other.

One great disadvantage of the wide field microscope is actually not demonstrated through the PSF shown in Fig. 2a, but it is emphasized when observing the optical transfer function (OTF). It is known as the problem of the missing cone in the OTF. This OTF tells us that for a uniform sample with a spatial in-plane frequency of zero, the microscope has no axial spatial-frequency response and an image is the same for in and out focus. The midfield OTF has the same band width as the confocal one, and therefore does not suffer from the wide field paradigm.

The transmitted light is a form of structured light. Due to frequency mixing between the structured light and the object, the sum and difference frequency exist [7] and are recorded in the image if they fall within the OTF. After recording multiple images, these higher frequencies are unmixed, resulting in a higher resolution image. When non-linear effects, as two photon excitation [15] or saturated excitation [8], are used the resolution can increase with the amount of high frequencies in the structured illumination. Then the only limiting factor is the signal to noise ratio of the higher frequency signals. In a later development stage this super-resolution technique can be used to enhance the resolution of the midfield

microscope beyond that of a confocal microscope, which has similar illumination spot size but no periodic structure.

3.2 Experimental setup

We intend to use the transmission through the hole-array for illuminating a biological sample. Both the large number of small illuminated volumes and the limited size of the volumes in the (predicted) transmission pattern are useful. The midfield microscope consists of the illumination, the sample/array and the collection part; its design is shown in Fig. 3. The illumination of the array is done with a laser (Oxxius, $\lambda=561$ nm, 50 mW). The array is made with a Focused Ion Beam, (FEI Technai) in 200 nm gold foil supported by 500 μm thick glass. The laser light impinges on the array from the glass side. Typical dimensions of the array are 65 by 65 holes with $d=150$ nm and $a=600$ or 650 nm. The sample is positioned on top of the array, hanging upside-down on a piece of glass. The emission of the excited fluorescent molecules labeling the sample is imaged through a high numerical-aperture oil-immersion lens (100x, NA=1.3) connected to an epi-fluorescence microscope (Leica BX-FM) and a CCD (Hamamatsu ORCA AG). This microscope allows observation of the full sample while fully illuminating in epi-fluorescence mode. A scan is required in the three perpendicular directions, because only a limited area is observed due to spatial distribution of the transmission and focus of the lens.

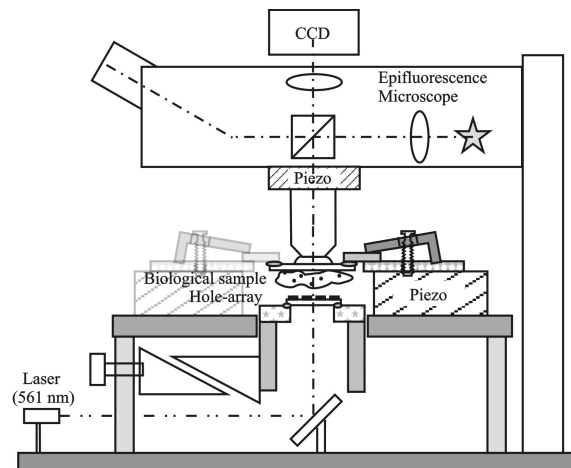


Fig. 3. The midfield microscope: collimated laser light passes through an array and excites fluorescent molecules labeling the sample; the fluorescent emission is captured with a CCD.

3.3 Scan in midfield and confocal microscope

The midfield and confocal microscope differ in illumination, detection and scan, but allow similar combination of different scans into the resulting image. The confocal microscope focuses the light transmitted through a pinhole onto the sample. This spot is scanned along the sample and the position of the spot is imaged by a detector through a pinhole. The midfield microscope produces illumination by transmission through a hole-array, the sample is scanned while the illumination is fixed and the image is recorded by a fixed CCD. Despite the differences, its resulting resolution and image formation are quite similar to the confocal microscope as shown in Fig. 4.

The distance between the spots in lateral direction is such, that they are imaged at isolated areas of the CCD, there is no overlap. The central pixel (in Fig. 4, white pixel labeled "C") of

the CCD camera in the midfield setup has a similar role as the pinhole in the confocal setup. It would be enough to use the light falling on this pixel for doing image formation. However, the surrounding pixels (grey pixel labeled “S”) also capture light and contain additional information. This extra information will be used to better estimate the pixel value of the central pixel by fitting a modeled PSF. The main result is either a higher signal to noise ratio (SNR) or an increase in resolution [16].

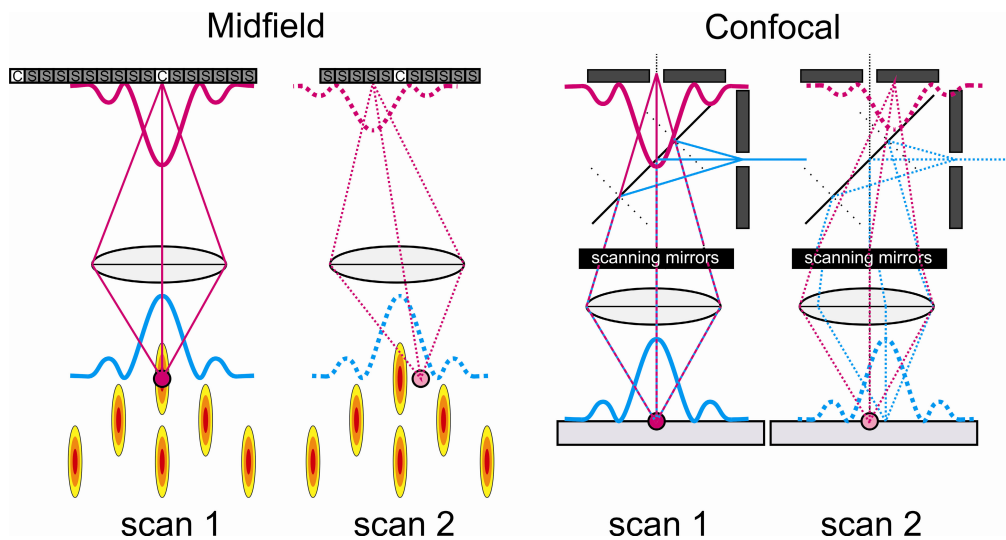


Fig. 4. Scan in the midfield and confocal microscope. The straight lines represent the light paths, blue for illumination and pink for emission, the solid line for the first and the striped line for the second position scanned. In the midfield microscope the sample, represented by a pink solid circle, moves and in the confocal the illumination moves. The sample is not optimally illuminated for both midfield and confocal at the second scan position, resulting in the image being centered outside the central pixel / pinhole and therefore a quadratic drop in intensity at the center pixel/ pinhole.

Scanning the illumination of the midfield microscope in a physical way (by moving the piezo stages) has possibly a few practical disadvantages, namely damage of the sample due to friction between array and sample, and a low scan speed. One possible solution is tilting of the illumination which results in a tilted transmission pattern.

3.4 Experimental results

Before measurements on real samples are done, the theoretical prediction has to be validated with experiments. We use a continuous homogeneous fluid, 20 μL of 50 μM Atto 565, on top of a hole-array with a period of 650 nm and circular holes and a diameter of 150 nm. Only the objective lens is scanned in z-direction, with steps of 100 nm and an acquisition time of 1 sec per image per plane. This time can be decreased if a higher power laser is used (>50 mW). Afterwards deconvolution is done and shading is removed, by dividing the image by its normalized Gaussian blurred version. The 12-bits images are linearly stretched between intensity levels of 2500 and 2800. This is somewhat overstretched for better visualization since its global minimal and maximal values are 2200 and 3000.

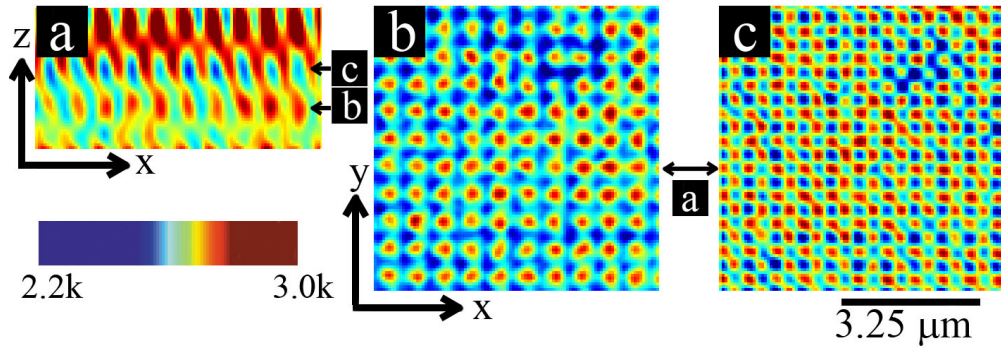


Fig. 5. Image of a fluorescent solution illuminated by transmission through a hole-array. It consists of stacked 2D images made by scanning the objective lens with steps of 100 nm. Shown are 2D cuts out of the 3D image with a) a typical xz plane and b,c) typical xy planes. The locations relative to each other are shown by the arrows indicating the other planes.

In Fig. 5 the fluorescent images reveal a highly distinct pattern, which repeats itself after certain height. When taken a cut through the xyz data (Fig. 5a), a qualitatively similar pattern is observed as was calculated in Fig. 1a. Note that this is the first time fluorescence is used in order to determine the transmission through an array. The transmission pattern in Fig. 5c shows large similarity with Near field Scanning Optical Microscope (NSOM) measurements [17-19]. However, when using the NSOM, the field pattern most likely changes as a result of the near-field tip, and the actual field pattern is therefore difficult to predict. As briefly discussed in paragraph 2.1, indeed we could use the 2D slit-arrays calculations from Fig. 1 to predict the 3D hole-array transmission [13].

The objective lens is scanned with steps of 100 nm, this can be translated into actual distances in the water. The required factor depends on the refraction index of the immersion oil and the water, and the numerical aperture. Theory predicts a factor of 0.38, but the actual value must still be verified experimentally.

4 CONCLUSIONS

A design for a new optical microscope, termed mid-field microscope, has been shown. It uses multiple illumination spots each of them comparable to the illumination achieved with a confocal microscope. The special illumination is achieved by using a unique nano-structure device of a nano-hole array structure in a gold foil. The physical properties of the transmission provide high-intensity well defined multiple illumination spots in three dimensions. Rigorous calculations of the transmission pattern of the hole-array, result in both a spectrum and a transmission pattern (while often only the spectrum is given), and indicate that for structured illumination, wavelengths smaller than the period are much more interesting. The scan and resolution are similar to the confocal, except for the use of multiple spots. When super resolution will be used, the resolution improves. The experimentally observed transmission pattern, which is the first published one measured by fluorescence in far-field, supports the theoretical predicts and are consistent with earlier reported NSOM measurements.

Acknowledgements

This work was partially supported by the Physics for Technology program of the Foundation for Fundamental Research in Matter (FOM), TNO and the Cyttron Consortium.

References

- [1] M. D. Egger and M. Petráň, "New reflected-light microscope for viewing unstained brain and ganglion cells," *Science* **157**, 305-307 (1967) [doi:10.1126/science.157.3786.305].
- [2] A. Ichihara, T. Tanaami, K. Isozaki, Y. Sugiyama, Y. Kosugi, K. Mikuriya, M. Abe, and I. Uemura, "High-speed confocal fluorescence microscopy using a Nipkow scanner with microlenses for 3-D imaging of single fluorescent molecules in real time," *Bioimages* **4**, 57-62 (1996).
- [3] P. J. Verveer, Q. S. Hanley, P. W. Verbeek, L. J. van Vliet, and T. M. Jovin, "Theory of confocal fluorescence imaging in the programmable array microscope (PAM)," *J. Microscopy* **189**, 192-198 (1998) [doi:10.1046/j.1365-2818.1998.00336.x].
- [4] R. Heintzmann, "Structured illumination methods," in *Handbook of Biological Confocal Microscopy 3rd ed.*, J. B. Pawley, Ed., Springer, Singapore (2006).
- [5] J. T. Frohn, H. F. Knapp, and A. Stemmer, "True optical resolution beyond the Rayleigh limit achieved by standing wave illumination," *Proc. Natl. Acad. Sci. USA* **97**, 7232-7236 (2000) [doi:10.1073/pnas.130181797].
- [6] R. Heintzmann, "Saturated patterned excitation microscopy with two-dimensional excitation patterns," *Micron* **34**, 283-291 (2003) [doi:10.1016/S0968-4328(03)00053-2].
- [7] M. G. L. Gustafsson, "Surpassing the lateral resolution limit by a factor of two using structured illumination microscopy," *J. Microscopy* **198**, 82-87 (2000) [doi:10.1046/j.1365-2818.2000.00710.x].
- [8] M. G. L. Gustafsson, "Nonlinear structured-illumination microscopy: Wide-field fluorescence imaging with theoretically unlimited resolution," *Proc. Natl. Acad. Sci. USA* **102**, 13081-13086 (2005) [doi:10.1073/pnas.0406877102].
- [9] T. W. Ebbesen, H. J. Lezec, H. F. Ghaemi, T. Thio, and P. A. Wolff, "Extraordinary optical transmission through sub-wavelength hole arrays," *Nature* **391**, 667-669 (1998) [doi:10.1038/35570].
- [10] H. A. Bethe, "Theory of diffraction by small holes," *Phys. Rev.* **66**, 163-182 (1944) [doi:10.1103/PhysRev.66.163].
- [11] H. J. Lezec, A. Degiron, E. Devaux, R. A. Linke, L. Martin-Moreno, F. J. Garcia-Vidal, and T. W. Ebbesen, "Beaming light from a subwavelength aperture," *Science* **297**, 820-822 (2002) [doi:10.1126/science.1071895].
- [12] *Partial Differential Equation Toolbox, for use with Matlab*, The Mathworks, Inc., Natick, MA.
- [13] E. Altewischer, M. P. van Exter, and J. P. Woerdman, "Polarization analysis of propagating surface plasmons in a subwavelength hole array," *J. Opt. Soc. Am. B* **20**, 1927-1931 (2003) [doi:10.1364/JOSAB.20.001927].
- [14] D. B. Shao and S. C. Chen, "Direct patterning of three-dimensional periodic nanostructures by surface-plasmon-assisted nanolithography," *Nano Lett.* **6**, 2279-2283 (2006) [doi:10.1021/nl061712b].
- [15] F. Helmchen and W. Denk, "Deep tissue two-photon microscopy," *Nat. Methods* **2**, 932-940 (2005) [doi:10.1038/nmeth818].
- [16] A. J. den Dekker and A. van den Bos, "Resolution: a survey," *J. Opt. Soc. Am. A* **14**, 547-557 (1997).
- [17] S. C. Hohng, Y. C. Yoon, D. S. Kim, V. Malyarchuk, R. Muller, C. Lienau, J. W. Park, K. H. Yoo, J. Kim, H. Y. Ryu, and Q. H. Park, "Light emission from the shadows: Surface plasmon nano-optics at near and far fields," *Appl. Phys. Lett.* **81**, 3239-3241 (2002) [doi: 10.1063/1.1515134].
- [18] D. S. Kim, S. C. Hohng, V. Malyarchuk, Y. C. Yoon, Y. H. Ahn, K. J. Yee, J. W. Park, J. Kim, Q. H. Park, and C. Lienau, "Microscopic origin of surface-plasmon

radiation in plasmonic band-gap nanostructures," *Phys. Rev. Lett.* **91**, 143901 (2003) [doi: 10.1103/PhysRevLett.91.143901].

- [19] R. Quidant, G. Badenes, S. Cheylan, R. Alcubilla, J. C. Weeber, and C. Girard, "Sub-wavelength patterning of the optical near-field," *Opt. Exp.* **12**, 282-287 (2004) [doi:10.1364/OPEX.12.000282].

Margreet W. Docter studies at Delft University of Technology. She obtained her BSc in 2000 and her MSc in 2003 on the topic of stability of a carbon nanotube as electron source for microscopy. She is continuing with her PhD at the Imaging Science and Technology department on the development of the midfield microscope, described in this article. Her current research interest is in the field of microscopy techniques, developing new ones or improving the existing ones.

Peter M. van den Berg received the degree in electrical engineering from the Polytechnical School of Rotterdam in 1964, the M.Sc. degree in electrical engineering, and the Ph.D. degree in technical sciences, both from the Delft University of Technology, in 1968, and 1971. From 1967 to 1968, he was employed as a Research Engineer by the Dutch Patent Office. Since 1968, he has been a member of the Scientific Staff of the Electromagnetic Research Group of the Delft University of Technology. He was appointed as a Full Professor in Electromagnetics in 1981. Since 2004, he is a Research Professor in the Faculty of Applied Sciences of the Delft University. His main research interest is the efficient computation of field problems using iterative techniques based on error minimization, the computation of fields in strongly inhomogeneous media, and the use of wave phenomena in seismic data processing. Major interest is in an efficient solution of the non-linear inverse scattering problem.

Paul F. Alkemade is associate professor at the Kavli Institute of Nanoscience in the Applied Sciences Department of the Delft University of Technology in the Netherlands. After graduating his Ph.D. at the University of Utrecht in 1987, he worked as an associate researcher at the University of Western Ontario in London Ont., Canada. His research interests include the interactions of particle beams with matter and the concurrent shaping and analysis of materials with particle beams. Previously, he has used and improved secondary ion mass spectrometry. At present, the interest is focused on shaping materials on the nanoscale.

Vladimir G. Kutchoukov is working as a research assistant in the group of Charged Particle Optics Groups in the faculty of Applied Sciences of the Delft University of Technology, The Netherlands since October 2006. After graduating his Ph.D. in the group of Laboratory for Electronic Instrumentation at the same university in the field of wafer level packaging in 2002 he worked for 3 years as a postdoc in same the group on a project for nanoscale electrophoresis for biomolecular applications. Afterwards before starting his current job he worked for 2 years as a process engineer in the R&D department at ASM Europe, The Netherlands.

Oana M. Piciu graduated in 2002 the Faculty of Biology and Geology, section Biology-Chemistry, Cluj, Romania. During her diploma project she studied the bio-reduction of a nitro-derivate of a phenothiazinic component using *Saccaromyces cerevisiae* cells. In the following year she attended the Master Courses at the same Faculty, section Cell Biology and Molecular Biotechnology, studying the cloning of a specific gene from *Bacillus subtilis* in *E. coli* cells. In present she is a PhD researcher within the Electronic Instrumentation Laboratory, Electrical Engineering Department of the Delft University of Technology,

investigating the process fabrication and testing of an atto-liter titer plate device for high speed molecular analysis like DNA hybridizations and protein immuno-assays.

Andre Bossche received the MSc degree in Electrical Engineering with honors in 1983, and the PhD degree in Electrical Engineering in 1988, both from Delft University of Technology, The Netherlands. He is associated professor at the Department of Microelectronics of the Delft University of Technology. He is leader of the Biodevices Research Group at the Laboratory of Electronic Instrumentation of the Delft Institute of Micro-Electronics and Submicron Technology (DIMES). He is author or co-author of 2 books and more than 100 scientific papers in journals and conference proceedings. His project group is engaged in research work on the subjects of reliability of integrated sensors and MEMS devices (in particular the reliability of microstructures and materials), micro- and nano- fluidic devices for (bio)-chemical analysis and sensors and microsystems for medical applications.

Ian T. Young is a Professor of Applied Physics in the Department of at Imaging, Science and Technology at Delft University of Technology (TU Delft). He received his BSc, MSc and PhD from Massachusetts Institute of Technology (MIT) in 1965, 1966 and 1969. From 1969 to 1979 he was an assistant and then associate professor at MIT. He has been a consultant to over 25 companies and government agencies in the United States and Europe. He has supervised more than 45 PhD thesis and 200 Master Theses. He is an author of over 175 major publications in refereed international scientific journals and scientific conferences. He has received awards for his research and teaching including the Leermester Prize of the TU Delft. His principle fields of expertise are Imaging Instrumentation, Image Processing (image in/image out), Image Analysis (image in/measurements out), Digital Signal Processing, Quantitative Microscopy, Lab-on-a-Chip Instrumentation, Automated and Analytical Pathology and Cytogenetics, and Pattern Recognition.

Yuval Garini is an assistant professor at the Physics Department and Nanotechnology Institute in Bar-Ilan University since January 2007. Previously he was with the Quantitative Imaging group, Imaging Science and Technology, Applied Sciences Department of the Delft University of Technology in Delft, The Netherlands. After graduating his Ph.D. at the Technion, Haifa Israel, he was one of the founders of a start-up company that developed a spectral imaging system and its applications to genetic testing and diagnostics. He is a member of the SPIE, ISAC and OSA organizations. His research interests include nano-based optical devices and its application to biological research, novel imaging methods for measuring the genome organization in the genome and single molecule studies.