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Super-resolution Imaging with Metamaterials for Cardiovascular Disease

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Abstract: We propose a novel TIRF-like microscope design with a metamaterial lens. The microscope's structured evanescent field with subwavelength patterns will breach the diffraction limit. With it we will study cell-matrix interactions, important in cardiovascular disease.

OCIS codes: (110.0180) Imaging Systems; (160.3918) Materials; (000.1430) General.

1. Introduction

Optical microscopy, particularly fluorescence microscopy, is still a primary method of imaging cells and their organelles [1]. Much progress has been made in developing different optical microscopy techniques, leading to techniques such as Confocal Microscopy and TIRF Microscopy, in order to meet the multivariate demands of biomedical imaging [2]. A primary aim has been improving the resolution of optical microscopy techniques, which is fundamentally limited as defined by the Abbe limit [3], in order to image and understand deep subcellular processes.

TIRF microscopy is an optical technique that uses an evanescent field, produced by a wavefront undergoing total internal reflection in the sample's substrate, to illuminate a thin section (~100-200nm) [2], of a sample with an exponentially decaying excitation field. This confined excitation improves upon the image resolution of optical microscopy by reducing background fluorescence. It is the principal technique for imaging the cell membrane and the process of endocytosis [1]. A promising super-resolution biomedical imaging technique is Structured Illumination Microscopy (SIM). The sample is illuminated with spatially structured excitation light – a periodic pattern. A series of such images is taken and are then processed to extract higher resolution information and generate a reconstruction with the improved resolution. However image acquisition is relatively slow [2]. The combination of TIRF and SIM has been investigated [4], and this project aims to build upon its progress to produce a super-resolution surface imaging technique.

The proposed microscope will use novel electromagnetic materials – metamaterials. Metamaterials can be defined as “an arrangement of artificial structural elements, designed to achieve advantageous and unusual electromagnetic properties” [5]. Therefore instead of a traditional material whose properties derive from its constituent atoms, a metamaterial derives its properties from its constituent structural elements or units. Consequently, materials with a negative refractive index are achievable, allowing for the potential of sub-diffraction limit optical imaging [6]. The proposed microscope will use a metamaterial lens to produce a TIRF-like evanescent field which will have a structured pattern, akin to SIM. As the fringes produced by the metamaterial are created by the surface plasmons, not an interference patterns in SIM, they are not diffraction limited, and the resulting excitation field is spatially confined as in TIRF, and can be structured as in SIM, but with a much higher spatial frequency.

2. Microscope Principles

The overall design of the proposed microscope is very similar to that of a brightfield microscope, the light travels in a straight line through the optical system, as opposed to the configuration of a TIRF microscope where the light must be incident on the sample substrate (usually a glass slide or cover slip) at an angle to produce an evanescent field. This is shown in cross-section in Figure 1a. . Light incident on the metalens produces a structured evanescent field from the far surface. The structured evanescent field then illuminates a thin slice of the sample, exciting fluorophores which then emit light which can be imaged in the far-field. The image of the fluorescence emission can then be reconstructed computationally to account for the structured excitation.

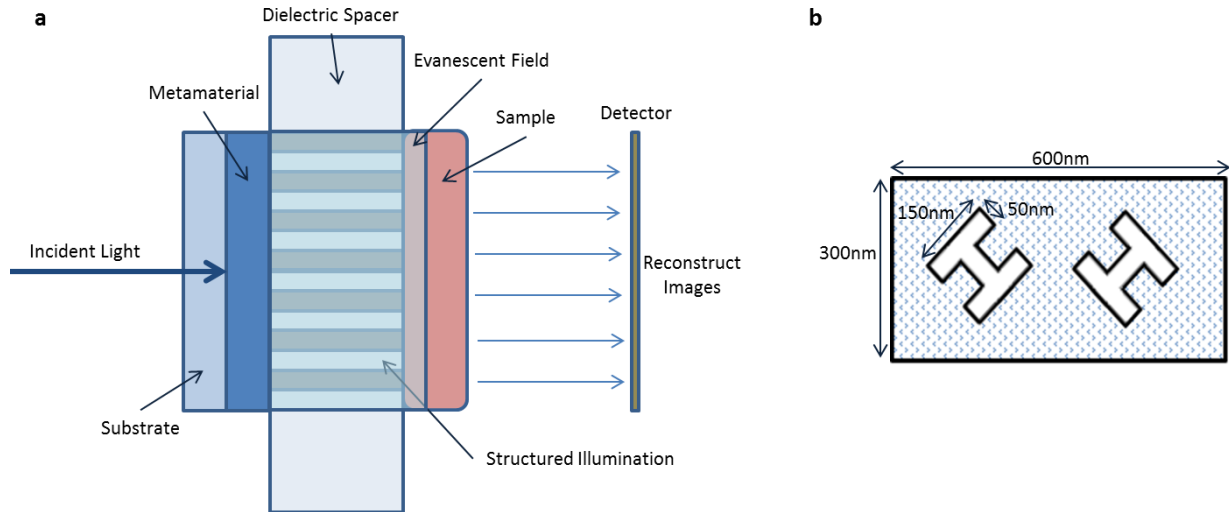


Figure 1. Schematic of: a - the proposed super-resolution microscope; b - the chosen metamaterial unit cell design, two ‘H’ shapes at $\pm 45^\circ$ to the normal. The metalens is formed from an array ($100 \times 100 \mu\text{m}$) of these unit cells.

3. Methodology - Simulations

Initial simulation work has been carried out in both MATLAB (Mathworks, Natick, MA) and CST Microwave Studio (CST, Framingham, MA). Simulations of the interaction of EM waves with different metamaterial designs and the image formation process have been conducted in CST-MWS to assess different potential designs of metalens. The electric field data from CST-MWS was then exported to and processed in MATLAB to determine the quality of the structured field produced. The design suggested by the simulation results is shown in Figure 1b, on the basis of which investigations into the feasibility of construction of a prototype metalens have begun. The proposed design consists of a unit cell design (two ‘H’ shapes at $\pm 45^\circ$ to the normal) cut from a gold film (Fig. 1b) which is reflected and tiled until the desired area is filled. The design is required to be symmetrical with a π phase difference between the two elements in order to produce the required structured field. Moreover the ‘H’ shape results in stronger field enhancement than a simpler shape, but is still relatively simple to manufacture.

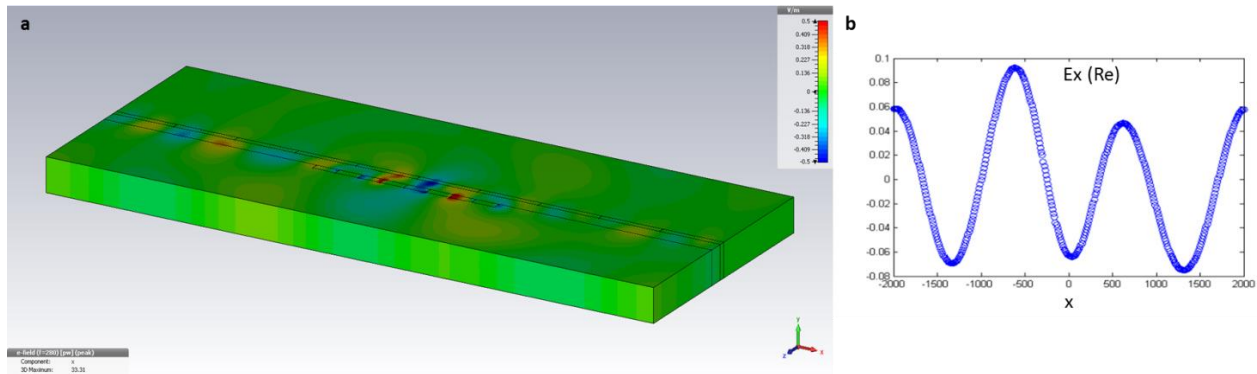


Figure 2. a – 3-dimensional colourmap of the x-component of the E-field at 280 THz for the metalens simulation with a grating sample. The x-component of the E-field is shown here as it is the main component of the overall E-field, due to the incident light being y-polarised which the metalens converts into predominantly x-polarised light; b – Plot of the real component of the x-component of the electric field data along a line in the x-direction at the end of the simulation volume ($y=0, z=2000\text{nm}$), processed in MATLAB. This corresponds qualitatively with the CST simulation.

4. Methodology – Constructing a Prototype Metalens

Preliminary prototypes were constructed in PMMA spin-coated onto a Silicon wafer. The metalens was produced using Electron-beam lithography using a Philips XL 30 Scanning Electron Microscope (field emission) with the Raith Elphy Plus E-beam hardware to interface with the SEM. The patterns were designed using the Elphy Quantum software. The final metalens will be constructed from a 40nm gold film sputter coated onto a glass slide, with a PMMA resist. The dielectric spacer will then be constructed on the metamaterial.

5. Results

Preliminary work has been conducted in order to build a prototype metalens based upon the chosen design, see fig. 1b. Initial tests to determine the feasibility of the design have been conducted using electron beam lithography with test samples of PMMA mounted on a silicon wafer. Initial attempts have shown great promise that the design will be achievable.

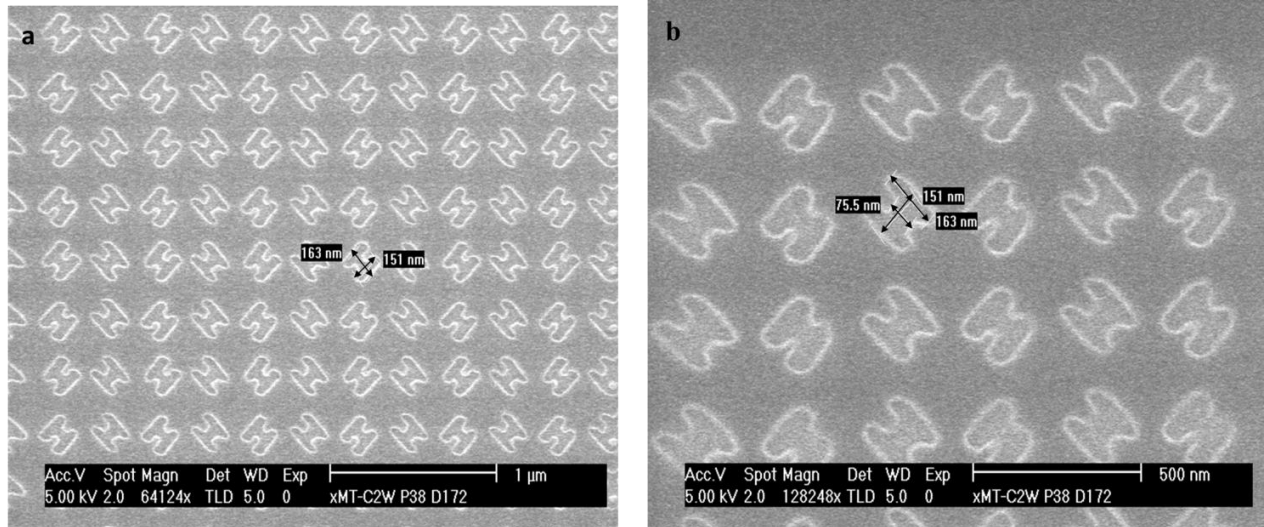


Figure 3. SEM images of: a –the unit cell array of ‘H’ shapes; b – zoomed in SEM image of the unit cell array of ‘H’ shapes.

It can be seen, see fig. 3, that superficially the shapes are fairly close to the intended design, although they are less sharp than desired. The effects on the evanescent field of the imperfections of the ‘H’ shapes are being characterised via CST-MWS simulations. Moreover, the final design once made in gold will be fully characterized. Indeed it can also be seen that the dimensions of the ‘H’ shapes are of the correct order of magnitude ($\sim 151 \times 163$ nm, should be 150×150 nm). However they are generally slightly larger than desired, and are especially large in the centre of the ‘H’ (~ 76 nm across, should be 50nm). This is caused by overexposure of the PMMA due to secondary electrons.

6. Conclusions

The chosen metalens design has been shown in simulation to produce a strong structured evanescent field. The same design, but with a smaller unit cell demonstrated even stronger field enhancement, but may not be feasible to construct. The prototype metalens is practically feasible and is being trialed in gold. The accuracy of the construction of the metalens will be tested by imaging it with electron microscopy, AFM and FT-IR spectroscopy. Its imaging potential will be then tested using an inverted brightfield microscope and a nano-structured sample of known shape and dimensions. The images will then be reconstructed and compared to the simulation data. The metalens design will then be optimised and eventually tested on biological samples, notably platelets and their surface proteins, to investigate their link to cardiovascular disease.

7. References

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