PHYSICS

Special Topic: Metamaterials

Metamaterial-assisted illumination nanoscopy

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Traditional optical microscopy resolves fine details of the microscopic worlds, but has its resolution limited by the wave nature of light. According to the Abbe diffraction limit $d = \lambda/2\mathrm{NA}$, where λ and NA represent the light wavelength and numerical aperture of the optics, respectively, the minimum resolvable distance d is typically ∼200 nm at visible frequencies.

Developments in super-resolution microscopy (SRM) go beyond the Abbe limit and reveal the nanoscale world optically. A few SRM technologies, such as stimulated emission depletion microscopy (STED), single-molecule-localization microscopy (SMLM) and structured illumination microscopy (SIM), are all well established (all commercially available) and are widely used to investigate biological phenomena that could not be seen before [1]. Resolution-wise, 1-nm localization accuracy has been achieved by MINFLUX [2], which brings together the coordinate-targeted locating method in STED and the stochastic approaches in photo-activated localization microscopy (PALM) or stochastic optical reconstruction microscopy (STORM), while, speed-wise, video-rate low-phototoxicity imaging with resolution ∼84 nm has been achieved by SIM [3].

Ingeneral, modern adaptations of SRM not only require high resolution, but also need to address the growing demands of imaging speed, low phototoxicity, imaging depth, number of color channels, simplicity of usage, system cost, etc. Apparently, there is no single solution to satisfy all the demands at the same time. Researchers, therefore, select the right ones from a variety of existing SRMs and adapt them for their specific needs. Meanwhile, it is always

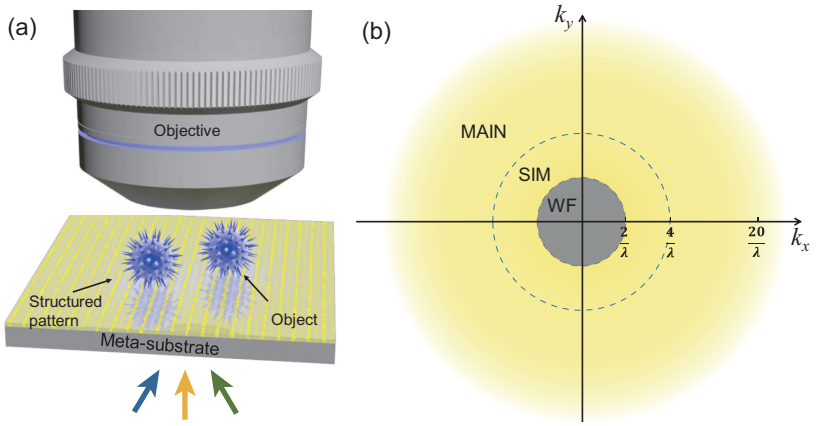

Figure 1. (a) Schematics of metamaterial-assisted illumination nanoscopy (MAIN). A meta-substrate shapes input light into a variety of nanoscale structured patterns depending on its wavelength and/or incident angle. The object, illuminated by these patterns in series, is imaged by a diffraction-limited widefield objective. A super-resolution image of the object is numerically reconstructed afterward. (b) Illustration of different imaging technologies in the spatial frequency domain (assume that NA = 1). WF: widefield microscopy; SIM: structured illumination microscopy.

appealing, challenging as well, to have one system to meet as many requirements as possible. For instance, when high temporal resolution, high spatial resolution and low phototoxicity are in demand simultaneously.

Initiated from the 'perfect lens' [4], the metamaterial-based 'superlens' provides a completely different way to beat the diffraction limit: The first superlens was demonstrated to project super-resolution images at near field [5]. Then the hyperlens [6] and metalens [7] brought the super-resolution images to far field through an intriguing magnification mechanism. Although the resolution of a hyperlens could be extended to ~10 nm scale and only bounded by the imperfection of the metamaterial, the real-world application is rather limited: the hyperlens typically has a small field of view due to its curved geometry.

Recent developments on metamaterial-based super-resolution imaging overcome that difficulty by merging it with structured illumination microscopy: metamaterial greatly extends the resolution of SIM, and has inherent advantages over SIM, including high temporal resolution and low phototoxicity. The new metamaterial-based super-resolution imaging techniques can be generally described as metamaterial-assisted illumination nanoscopy (MAIN), and are schematically illustrated in Fig. 1. A piece of metamaterial is integrated into a substrate to hold objects under a widefield microscope. The metamaterial substrate (meta-substrate) shapes incident light into nanoscale structured patterns. By collecting diffraction-limited images of an object illuminated by a series of these structured patterns, MAIN can reconstruct a super-resolution image through modified SIM algorithms.

In SIM, the resolution is about twice the diffraction limit of an objective lens (order of $\lambda/4$). MAIN, while its detection remains diffraction-limited, extends the resolution by projecting diffraction-unlimited illumination patterns. A meta-substrate should be designed to fulfill two major requirements for MAIN operation: firstly, it should produce deep sub-diffraction-limited light patterns; secondly, there should exist a tuning method to switch and/or shift those structured light patterns.

For instance, the meta-substrate can consist of a periodic plasmonic structure. This method, called plasmonic structured illumination microscopy (PSIM), excites the object by the interference patterns from two or multiple propagating surface plasmon waves and improves resolution to $\sim\lambda/5$ [8]. The resolution can be further extended to $\sim\lambda/6$ in localized plasmonic structured illumination microscopy (LPSIM) by introducing a meta-substrate that consists of an array of localized plasmonic resonators [9]. The incident angle of the laser beam is used to shift the structured patterns in both cases.

Another promising design of meta-substrate is based on a hyperbolic metamaterial (HMM). In [10], a configuration called hyperstructured illumination is introduced. The HMM is made by stacks of thin metal and dielectric films, which will grant a theoretical resolution close to the thickness of its unit cell, thus achieving resolution beyond $\lambda/40$ [11]. To generate the structured light pattern, periodical or random nanostructures [12] on a metallic or opaque mask, through which light will be shaped, are attached to one side of the HMM substrate. To have the pattern scanned, the input wavelength is tuned so that the structured light patterns will appear to be different after they travel through the highly dispersive HMM and illuminate the object.

In addition to the extended resolution, the meta-substrate is also capable of making fluorescent dyes emit more photons through the Purcell effect. For a given fluorescent molecule, there is a total number of photons to be collected before it bleaches, known as its lifespan, which results in an inevitable trade-off between signal/noise ratio and bleaching rate. Interestingly, the Purcell effect from plasmonic structures or metamaterials has been shown to greatly enhance the spontaneous emission rate, leading to a prolonged lifespan of fluorescent molecules. In [13], about a 1000-fold increase of harvested photons is reported by making a fluorescent molecule close to a plasmonic nano-antenna. This represents a unique advantage of MAIN for greatly reduced phototoxicity.

Allied with SIM, the metamaterial-assisted illumination nanoscope will have a great potential in high-spatiotemporal-resolution surface imaging. Unlike localization-based SMLM or point-scanning STED microscopy, MAIN needs a minimum number of camera frames to reconstruct a widefield super-resolution imaging. Ideally, a 250-nm

diffraction-limited system with an imaging resolution of 25 nm only requires $(250/25)^2 = 100$ frames. Gaining resolution from its metamaterial-shaped illumination, MAIN is free from the need to select fluorescent dyes and is capable of working under low illumination intensity (~5 W/cm^2 [9]). It will provide much smaller photon doses than either STED (1–200 MW/cm^2 [1]) or SMLM (1–10 kW/cm^2 [1]), which is beneficial for addressing photobleaching/phototoxicity problems.

The MAIN result published so far, however, is still preliminary. For instance, very high resolution (20–50 nm) MAIN has yet to be experimentally demonstrated. The combination of low phototoxicity through the Purcell effect in super-resolution MAIN has only been indirectly proved. Other issues, such as the biocompatibility of those metasubstrates, also need to be investigated. Nevertheless, MAIN uniquely addresses three of the most important imaging aspects simultaneously: resolution, frame rate and phototoxicity, opening up tremendous new opportunities for future developments and applications.

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