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Structured illumination microscopy and its new developments

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Optical microscopy allows us to observe the biological structures and processes within living cells. However, the spatial resolution of the optical microscopy is limited to about half of the wavelength by the light diffraction. Structured illumination microscopy (SIM), a type of new emerging super-resolution microscopy, doubles the spatial resolution by illuminating the specimen with a patterned light, and the sample and light source requirements of SIM are not as strict as the other super-resolution microscopy. In addition, SIM is easier to combine with the other imaging techniques to improve their imaging resolution, leading to the developments of diverse types of SIM. SIM has great potential to meet the various requirements of living cells imaging. Here, we review the recent developments of SIM and its combination with other imaging techniques.

Keywords: Structured illumination microscopy; diffraction limit; super-resolution.

1. Introduction

Recently, the optical microscopy has become an indispensable tool in biological and medical research field. Optical microscopy provides a powerful method for researchers to observe the microscopic biological world. However, the imaging resolution of the optical microscopy is limited by the light diffraction, which is called Abbe diffraction limit[1] ($d = 0.61\frac{\lambda}{\mathrm{NA}}$, λ is the wavelength of light, NA stands for the numerical aperture of the microscope objective lens). That is to say, the structure of the sample, which is smaller than the diffraction limit,

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is unresolvable under the optical microscope observation.

In the past two decades, many attempts to break the diffraction limit to obtain super-resolution have achieved great progress in the fluorescence imaging field. Researchers have developed several super-resolution fluorescence microscopy, such as, stimulated emission depletion (STED) microscopy,[2] structured illumination microscopy (SIM),[3] stochastic optical reconstruction microscopy (STORM)[4] and photo-activated localization microscopy (PALM).[5] Although the resolution improvement of SIM is less than that of the other super-resolution techniques, the sample requirements of SIM are not as strict as the other super-resolution methods. Unlike PALM/STORM that require specialized photo-switchable labeling, SIM can use common fluorophores with no special properties, and another advantage of SIM is that low illumination intensity (1–100 W/cm^2) can be used, which is important for imaging living cell. With low illumination intensity, the fluorophores experience less photo-bleaching. Besides, structured illumination is easier to combine with the other imaging techniques to improve their imaging resolution. Therefore, many researchers devoted to the SIM technique development and its application research. Although several researchers have published reviews on the advancements of super-resolution fluorescence microscopy,[6–8] including SIM,[9] this paper will focus on the development of SIM and its combination with other imaging techniques.

2. The Understanding of SIM

2.1. *Two-dimensional linear SIM*

The use of structured illumination to obtain super-resolution information can be explained in the context of the "spatial frequency" of an image. The optical microscopy can be regarded as a low-pass filter in reciprocal (frequency) space. The schematic diagram of frequency spectrum expansion by structured illumination is shown in Fig. 1. The pentagon stands for the spectrum information of the sample. Figure 1(a) represents the optical transfer function (OTF) of common wide-field fluorescence microscopy, and the high frequency information,

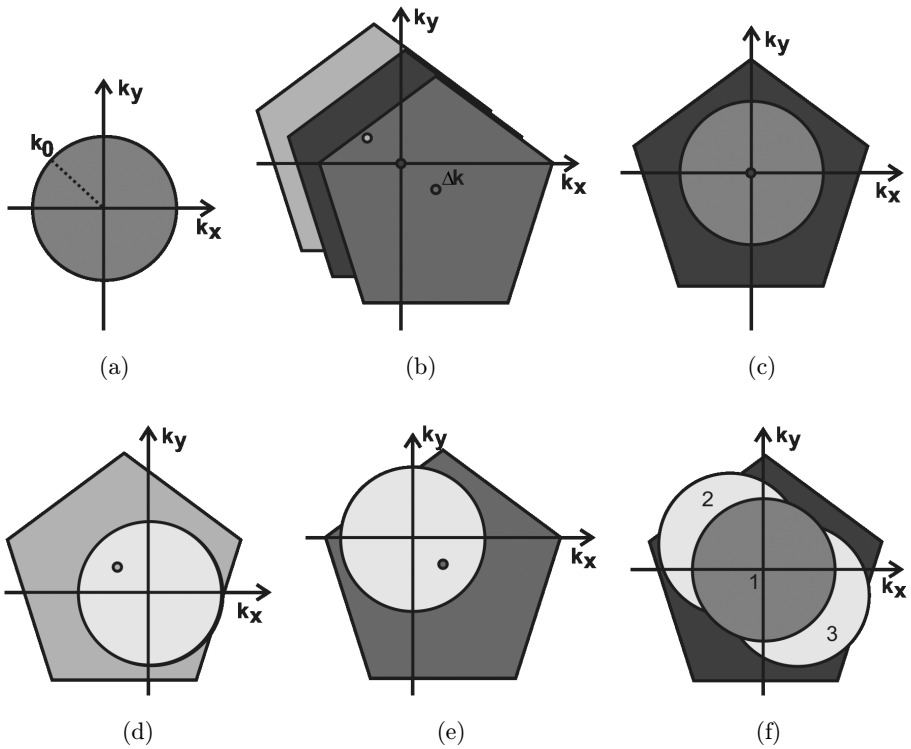


Fig. 1. Schematic of frequency spectrum expansion by structured illumination. (a) The OTF of common fluorescence microscopy, (b) is superposition of three frequency spectra components by structured illumination, (c)–(e) are three components of frequency spectra, multiplying the OTF, separating from each other, moving to the corresponding place, respectively, (f) addition of the three components of frequency spectra, having been moved to the corresponding place.

which is higher than the cutoff frequency k_0 of the microscopy, is lost after light passes through the optical microscope.

Three superimposed frequency spectrum components can be produced by structured illumination, shown in Fig. 1(b). According to optical imaging theory, the three mixed components are multiplied by the OTF, and then we separate them from each other and move them to the correct position through image processing, as shown in Figs. 1(c)–1(e). To separate the three components, a set of three images with illumination phases shifted by steps of $2\pi/3$ is required. Figure 1(c) is the separated zeroth-order frequencies components, and Figs. 1(d) and 1(e) are the ± first-order components. The three frequency spectrum components are superposed to extend the region of the frequency space, shown in Fig. 1(f). Accordingly, when using structured light to illuminate the sample, we can obtain the sample structure information from three superimposed frequency information. The observable frequency region contains not only the usual information (region 1 in Fig. 1(f)), but also information that originates in two offset regions (regions 2 and 3 in Fig. 1(f)), which is not available in a conventional microscope. That is to say, with structured illumination, the high frequency information of the sample is encoded into the low frequency region to make it pass through the optical microscope, and then we decoded the mixed frequency information to recover the high frequency information, therefore extending the observable frequency region of optical microscope. High resolution objects in real space carry high spatial frequencies in reciprocal region, while low-resolution objects have low spatial frequencies. Expansion of the frequency region means the resolution improvement.

The above schematic diagram only shows one single direction spectrum expansion with structured illumination. Taking inverse Fourier transform of this extended spectrum, we can only obtain the image with one-direction resolution improvement. In order to obtain isotropic resolution improvement, we usually need to obtain two- or three-direction structured illumination images, shown in Fig. 2. The frequency spectrum expansion of two orthogonal directions structured illumination pattern is shown in Fig. 2(a), while three patterns direction with $\pi/3$ interval is shown in Fig. 2(b). The resolution improvement of SIM is linearly proportional

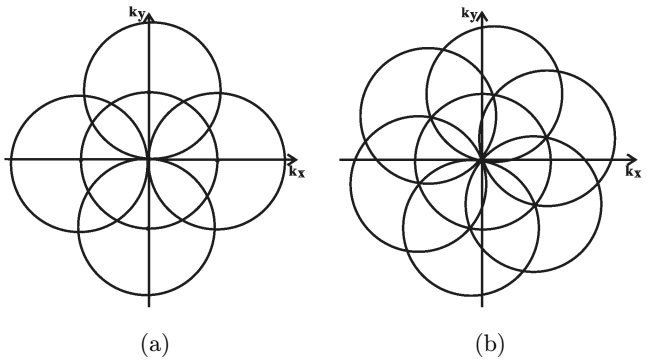
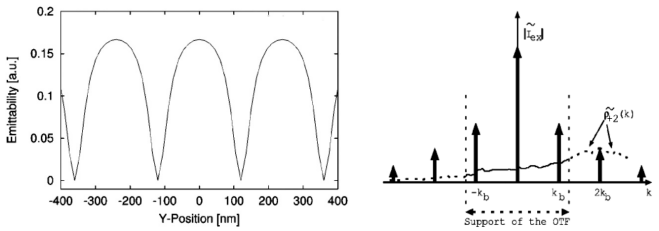


Fig. 2. Schematic diagram of frequency spectrum expansion with several pattern orientation. (a) 0° and 90° orthogonal illumination patterns direction, and (b) three patterns direction with $\pi/3$ interval.

to the frequency of the sinusoidal pattern (Δk in Fig. 1(b)). Since the maximum spatial frequency of the sinusoidal pattern is also limited by the diffraction limit of the imaging system, the maximum frequency spectrum expansion of structured illumination is only twice that of the traditional fluorescence microscope. Thus, the maximum improvement of resolution by structured illumination is a factor of two.

2.2. *Two-dimensional nonlinear SIM*

As the maximum resolution enhancement with linear structured illumination is a factor of two. The researchers proposed nonlinear SIM in order to further improve the resolution, and the nonlinear SIM was first achieved by fluorescent saturation. In the process of fluorescence excitation, the fluorescence intensity is proportional to the excitation light intensity. When the intensity of the excitation is a sinusoidal function, the fluorescence intensity is also a sinusoidal function. With the increase of the excitation light intensity, the first excited state of the fluorescent molecule is saturated, and the fluorescence intensity distribution is no longer a sinusoidal function, as shown in Fig. 3(a). Therefore, the saturated fluorescence intensity distribution generates a series of nonlinear terms in the frequency domain, as shown in Fig. 3(b), and the spatial frequency of these nonlinear terms are the second harmonic, three harmonic or higher order harmonic frequency of the spatial frequency of linear structured illumination, which depends on the excitation light intensity (saturated degree of fluorescent molecules in the first excited state). Accordingly,



(a) (b)

Fig. 3. Fundamental concept of nonlinear SIM implemented by fluorophore saturation.[10] (a) Fluorescence intensity distribution in real space with high-intensity illumination leading to fluorophore saturation. (b) Corresponding emittability pattern in Fourier space.

these nonlinear higher order spatial frequency terms further extend the OTF, making the more information of the higher spatial frequency shifting into the observable OTF, as shown in Fig. 4. It is noted that fluorescent saturation is the only way to achieve nonlinear effect, and reversible photo-activation of molecules can also be used to perform nonlinear SIM for higher resolution.

2.3. *Three-dimensional linear SIM*

For a conventional optical microscope, the three-dimensional OTF is a torus-like region, as shown in Figs. 5(a) and 5(b), and the "hole" of the torus is the "missing cone" of information near the k_z-axis, and to extend the resolution is equivalent to finding a method to detect information that is outside of this observable region.

The principle of three-dimensional SIM is similar to the two-dimensional SIM. In the three-dimensional SIM, the specimen is illuminated with three mutually coherent beams, as shown in Fig. 5(c). The interference between the three illumination beams generates a three-dimensional excitation pattern that includes seven Fourier components at each difference vector between the three illumination wave vectors, as shown in Fig. 5(d). The observable region that becomes accessible with this illumination pattern is the convolution of the seven-dot illumination structure of Fig. 5(d) with the conventional OTF in Figs. 5(a) and 5(b), resulting in the region, shown in Fig. 5(e). However, it extends lateral resolution only in one direction, the

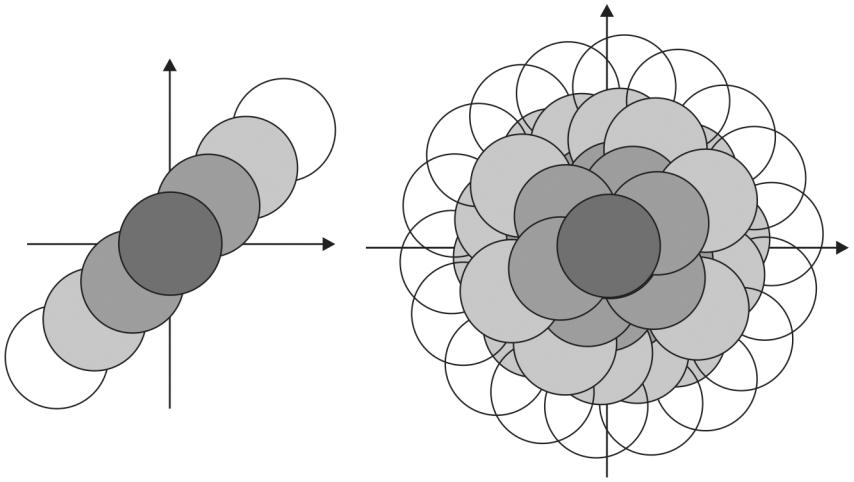
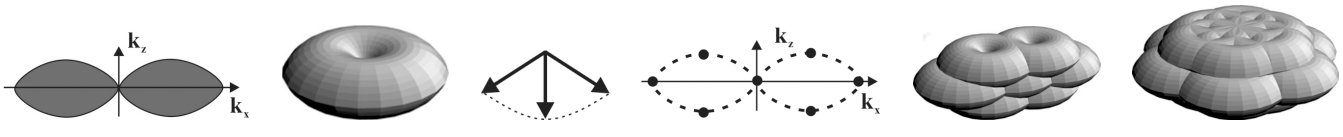


Fig. 4. The OTF extension by nonlinear structured illumination.[11]



(a) (b) (c) (d) (e) (f)

Fig. 5. Extension of the observable region of reciprocal space through three-dimensional structured illumination.[12] Observable regions for (a) and (b) the conventional microscope. (c) The three amplitude wave vectors corresponding to the three illumination beam directions. (d) The resulting spatial frequency components of the illumination intensity for three-beam, and observable regions of three illumination beams in one (e) or three (f) sequential orientations.

procedure can be repeated with the illumination pattern rotated to other orientations. Figure 5(f) exhibits the observable region using three illumination pattern directions. This region fills in the missing cone while maintaining the full factor of two of lateral resolution enhancement, and doubles the axial resolution as well.

3. The Development of the SIM Super-Resolution Technique

3.1. *The main development of SIM by two study groups*

The pioneers of SIM super-resolution imaging technique are Heintzmann and Gustafsson. In 1999, Heintzmann and Cremer first proposed the concept of laterally modulated excitation microscopy (LMEM),[13] which is later known as SIM. They described the physical principle and image reconstruction steps to realize super-resolution image in detail. In 2000, Gustafsson *et al.* presented SIM,[14] and they showed the imaging results with ~ 115 nm spatial resolution, which is twice the diffraction limited resolution.

The linear structured illumination can only achieve two times resolution enhancement. In 2002, the Heintzmann *et al.*[10] first proposed the saturated patterned excitation microscopy (SPEM). They used saturated fluorescence excitation to achieve nonlinear fluorescence excitation so as to obtain higher spatial frequency information, therefore further improving the spatial resolution. In the following year, Heintzmann reported a two-dimensional excited saturation excitation microscopy.[15] By using of two-dimensional grating to produce two-directions structured illumination, simulation result with 57 nm resolution were obtained through computer simulation. In 2005, Gustafsson experimentally confirmed that saturated structured illumination can further improve the spatial resolution. They obtained experimental results with ~ 50 nm spatial resolution, and termed the method as the saturated structured illumination microscopy (SSIM).[11] The saturated fluorescence excitation needs very high excitation intensity, and high excitation light intensity could cause severe sample photo-bleaching, thus, hindering the application of this technique in the study of biological samples. In order to reduce the nonlinear excitation power, using the photo-switchable fluorescent protein to replace the fluorescent saturation method to realize the nonlinear structured illumination was first reported by Heintzmann group.[16] It is a pity that they did not present good biological experimental results. In 2012, Gustafsson team used the same method to generate nonlinear structured illumination and showed the experimental results of biological samples with ~ 50 nm spatial resolution.[17] The required excitation light power decreased six-orders of magnitude than that of saturated fluorescence excitation. In 2015, Li *et al.*[18] proposed patterned activation nonlinear SIM to improve the imaging speed of nonlinear SIM.

In 2008, Gustafsson team first achieved three-dimensional structured illumination super-resolution fluorescence microscopy, doubling both the lateral and axial resolution.[12] In the same year, the research team also combined structured illumination with the I^5M technique[19] and proposed the concept of I^5S. They demonstrated the results with all the three-dimensional resolution at 100 nm.[20] However, a physical grating was initially used to generate structured illumination, and mechanical translational or rotational of the grating were needed to generate stripe patterns with various phases and directions. Therefore, the method had low temporal resolution, and was limited to fixed samples imaging. In 2009, the two groups have both used a spatial light modulator (SLM) to replace the initial physical grating to generate structured illumination, achieved two-dimensional super-resolution imaging of living cells.[21,22] Without any mechanical movement of the optical element, they greatly enhanced the switching time between the different illumination styles, enabling live cell super-resolution imaging. In 2011, Gustafsson *et al.*[23] have also realized the super-resolution imaging of three-dimensional living cells. In 2012, the same team introduced two-color imaging method into the three-dimensional structured illumination live cell imaging technique, and they demonstrated the results with two-color three-dimensional super-resolution imaging of living cells.[24]

3.2. *The enhancement of SIM by other researchers*

The above two groups have made pioneering work in the SIM super-resolution imaging field, and they continued to develop this method, and achieved main improvement of the SIM super-resolution

imaging technique, meeting the various needs of biological research. Besides the two teams, many other researchers were also engaged in the improvements and developments of SIM super-resolution technique. Chung *et al.*[25] first combined structured illumination with the total internal reflection fluorescence (TIRF) microscope and put forward standing wave-TIRF (SW-TIRF) (SW: standing wave represents structured illumination) method. Fiolka *et al.*[26] further developed the TIRF-based SIM technology, they used an SLM to generate structured illumination, so that the phase and direction of the structured illumination can be easily switched. Gliko *et al.*[27,28] used four acousto-optic deflectors, (AOD) to achieve the SW-TIRF, and the strips can be changed in milliseconds because of the rapid scanning capabilities of AOD. In 2009, Zhang *et al.*[29] used an SLM to generate four-direction structured illumination. Compared with the commonly used two or three illumination directions, it achieved better isotropic resolution enhancement. In 2011, Wang *et al.*[30] combined structured illumination with aplanatic solid immersion lenses-based fluorescence microscopy. As the solid immersion lens itself has very high NA, the combination can generate a wide-field high-resolution imaging system with bandwidth corresponding to an NA of three. In 2013, Dan *et al.*[31] used LED as the light source and digital micromirror device (DMD) to produce structured illumination. They showed the super-resolution capability and sectioning ability with structured illumination, respectively. Their experimental setup has several advantages, such as, low cost, easy switching of multiple wavelength and free of speckle noise. In 2012, York *et al.*[32] presented multifocal SIM (MSIM). MSIM used a DMD to generate sparse 2D excitation patterns and digital processing after acquisition to obtain optically-sectioned images with ~ 145 nm lateral and ~ 400 nm axial resolution at 1-Hz frame rate. Mudry *et al.*[33] reported a blind-SIM that super-resolution information can be made available by illuminating with several uncontrolled speckle patterns.

3.3. *Structured illumination combination of the other fluorescence imaging techniques*

The SIM original design is based on wide-field fluorescence microscopy. However, structured illumination can also be combined with line scanning imaging techniques. In 2009, Kim *et al.*[34] applied structured illumination to the conventional slit (line)-scanning confocal microscope to improve its lateral resolution. They presented the simulation results with lateral resolution enhanced by 1.43-fold compared with confocal microscopy. In 2012, Heintzmann group proposed line scan-SIM for imaging thick fluorescence samples,[35] using line scanning mode to exclude the background fluorescence from the thick sample, thus ensuring image quality of the thick samples.

3.4. *Structured illumination combination of the other non-fluorescence imaging techniques*

The above-mentioned advances of SIM super-resolution imaging is based on fluorescence imaging. In 2007, Littleton *et al.*[36] first proposed to apply the structured illumination to nonfluorescent imaging applications to achieve super-resolution imaging. In 2010, Hajek *et al.*[37] tried to combine structured illumination with coherent anti-Stokes Raman scattering (CARS) microscopy, however, they only reported the computer simulation super-resolution results without experiment results, and super-resolution imaging with structured illumination has been extended to the scattered light imaging systems. In 2011, Zhang *et al.*[38] used SLM to achieve three-dimensional structured illumination scattered light super-resolution imaging, assisted by gold nanoparticles. In 2012, Chowdhury *et al.*[39] proposed a structured oblique illumination microscope for nonfluorescent coherent scattering samples super-resolution imaging. In 2013, Chen *et al.*[40,41] reported a structured illumination differential interference contrast (SI-DIC) microscopy, achieving lateral resolution enhancement twice that of conventional DIC microscopy.

4. Conclusions

In the last two decades, the SIM technique has been greatly developed. The improvement of main technical parameters of SIM, have been achieved by two research teams, Heintzmann and Gustafsson groups. They improved the spatial and temporal resolution of SIM, and developed three-dimensional super-resolution imaging and multicolor imaging.

The other researchers contributed to the SIM development were mainly by exploiting different methods to realize structured illumination or combining structured illumination with the other imaging techniques. These techniques includes TIRF, confocal fluorescence microscopy and the other nonfluorescence imaging methods, such as CARS, DIC and scattered light imaging. The combination of SIM with the other imaging techniques to improve their imaging resolution is also one direction of further development of SIM, and the other direction is to apply current-developed SIM super-resolution imaging to biological and medical research to obtain new information that are not available before.

Acknowledgments

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