Optical phase conjugation (OPC) for focusing light through/ inside biological tissue

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Abstract: Optical phase conjugation (OPC) is a technique that generates a light field with reversed wavefront and identical amplitude distribution as the incident light. It has a unique feature of suppressing the aberration of incident beam induced by inhomogeneous or disturbing medium. Although this technique has been extensively studied since the 1970s, it has become more attractive because of unprecedented achievements and prospective potentials in biomedical applications. OPC-based techniques have been successfully utilized to form a focus through/inside highly scattered biological samples. It opens a new avenue by significantly enhancing the light delivery in biological tissue for high-resolution imaging, diagnosis and treatment of medical diseases. In order to provide insight into its further development, recent progress of OPC techniques for focusing light through/inside biological tissue was summarized.

Key words: optical phase conjugation; holography; digital holography; holographic material; phase conjugate mirror

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0 Introduction

Optical phase conjugation (OPC) is a technique that could precisely reverse both the direction of propagation and the overall phase factor for each plane wave in an arbitrary beam of light. The process has been regarded as a unique kind of "phase conjugate mirror" (PCM) with very unusual image-transformation properties [1]. A PCM is like a regular mirror, in that it reflects incident light back towards where it came from, but it does so in a different way than a mirror reflection. In a regular mirror, light that strikes the mirror normal to its surface, is reflected straight back the way it came, as shown in Fig.1(a). This is also true for PCM. When the light strikes a normal mirror at an angle, it reflects back in the opposite direction, such that the angle of incidence is equal to the angle of reflection. In a PCM, on the other hand, light is always reflected straight back the way it came from, no matter what the angle of incidence, as shown in Fig.1(b).

This difference in the manner of reflection has significant consequences. If we place an irregular medium in the path of a beam of light, the parallel rays get distorted in certain directions, and after reflection from a regular mirror, each ray of light is bent even farther, as shown in Fig.1(c). With a PCM, on the other hand, each ray is reflected back in the direction it came from. The reflected conjugate wave therefore propagates backwards through the distorting medium, and essentially cancel the distortion, and returns to a coherent beam of parallel rays travelling in the opposite direction[2].

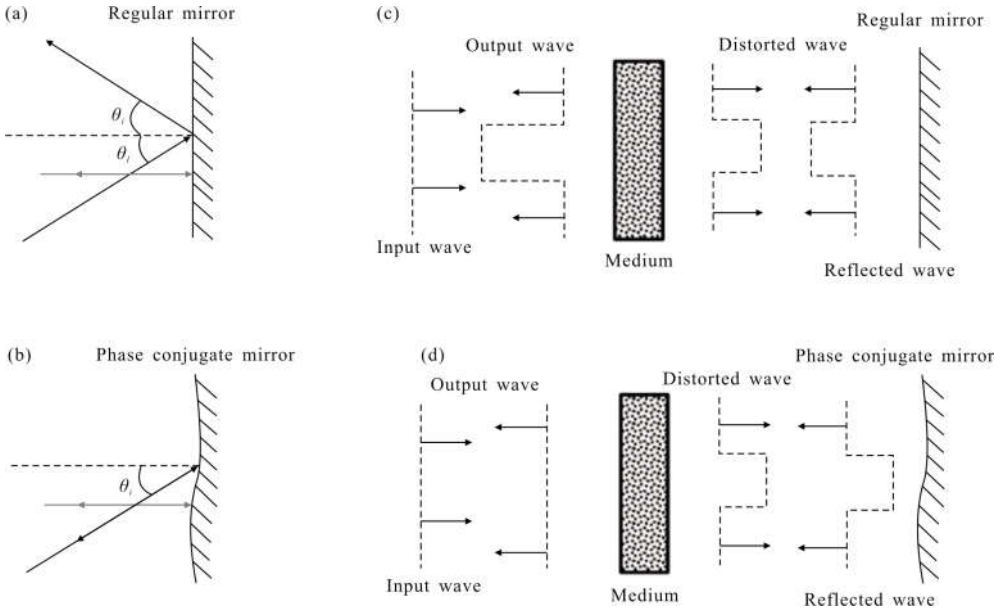

Fig.1 Comparison of a regular mirror and a phase conjugation mirror

With the above ray retracing property, it could be obviously seen that through OPC, a high-quality optical beam can be double passed through a disturbing object with no loss in beam quality. Since the cancellation of propagation distortion was demonstrated in the 1970s[3-4], OPC has been applied to numerous applications, such as laser resonators[5-6], imaging processing[7-8], optical transmission in fibers[9-10] and pulse compression[11-12]. In recent decade, OPC becomes more attractive in suppressing turbidity induced by biological samples, especially its ability of producing a controllable focus inside TM when combining with other techniques[13-14]. As it is well known, the imaging depth of all forms of focusing

optical microscopy is limited to less than one transport means free path because of multiple scattering in biological tissue[15]. Facilitating light focusing beyond the light diffusion limit, with the desired speed and localization, can profoundly benefit studies involving biomedical imaging, photon-induced biological manipulation and therapy.

Generally, two types of PCMs were demonstrated to implement OPC for biomedical applications. One utilizes the nonlinear response of material to record the information of scattered field and then produce the conjugate wave. The other reconstructs the conjugated wavefront by measuring the phase of distorted wavefront with digital devices. In this paper, a brief review of two OPC methods that has been demonstrated on focusing through/into TM is summarized and compared for their future development.

1 Principle of OPC-based focusing through/inside biological tissue

Optical phase conjugation (OPC) for suppressing scattering from biological tissue is usually referred to describe the wavefront reversion property of a backward propagating optical wave with respect to a forward propagating wave[1]. To describe two different processes between phase conjugate and conventional mirror in Fig.1(d) mathematically, we assume that the initial input wave is an ideal plane wave expressed by $\vec{E}(x,y,z,\omega)=E_0(x,y,z)e^{ikz}e^{-i\omega t}$. After passing through a disturbing medium it becomes:

$$\vec{E}'(x,y,z,\omega)=E_0(x,y,z)e^{i[kz+\varphi(x,y,z)]}e^{-i\omega t} \quad (1)$$

wherein z is the longitudinal variable along the propagation direction, x and y are the radial variables along the beam section, ω is the circular frequency of the optical field, $k=2\pi n_0/\lambda$ is the corresponding wave vector, n_0 is the refractive index of the propagating medium, $E_0(x,y,z)$ is the real amplitude function, and $\varphi(x,y,z)$ is a phase function describing the aberration influence on the wavefront from the disturbing medium.

If there is an ordinary plane mirror as shown in Fig.1(b), the reflected wave will be $\vec{E}_M'(x,y,z,\omega)=R_M\cdot E_0(x,y,z)e^{i[-kz+\varphi(x,y,z)]}e^{-i\omega t}$, then after passing back through the same medium the output wave can be written as:

$$\vec{E}_M''(x,y,z,\omega)=R_M\cdot E_0(x,y,z)e^{i[-kz+2\varphi(x,y,z)]}e^{-i\omega t} \quad (2)$$

In which, R_M is a real constant representing the reflectivity of the mirror. In this case, the aberration influence for two passes will be doubled.

On the other hand, if there is a phase conjugate reflector, as shown in Fig.1(c) and 1(d), the reflected wave can be expressed as:

$$\vec{E}_{PCM}'(x,y,z,\omega)=R_{PCM}\cdot E_0(x,y,z)e^{i[-kz-\varphi(x,y,z)]}e^{-i\omega t} \quad (3)$$

where R_{PCM} is the effective amplitude reflectivity of the phase conjugate reflector. In this case, after passing back through the same disturbing medium the output wave will be:

$$\vec{E}_{PCM}''(x,y,z,\omega)=R_{PCM}\cdot E_0(x,y,z)e^{-ikz}e^{-i\omega t} \quad (4)$$

Here, we see an ideal output plane wave, and the aberration influence from the disturbing medium can be entirely removed.

Various experimental techniques are available to implement OPC and generate the above phase-conjugated wave[2,16]. Based on the category of PCM, two types of techniques have been demonstrated to realize OPC for focusing through/into biological tissue. One type of PCM is based on holographic properties of material and the other relies on digital devices that have the ability of phase modulation to incident optical field. Strictly speaking, current material-based or digital techniques for OPC has the ability of generating phase-conjugated wave but is not a PCM with a reflection speed as fast as a flat mirror. Many earlier OPC techniques related to nonlinear optical processes with faster response time, such as degenerate four-wave mixing[9,17], backward stimulated scattering[18] and stimulated Raman scattering[19], has not been applied on thick biological tissue due to low reflected phase-conjugated wave for weak incident light. Therefore, this paper mainly focuses on those

OPC techniques that hold promise for focusing light through and inside biological tissue.

2 Holographic material-based OPC technique

Preserving the information of incident optical field with holographic material is a traditional and effective way to realize OPC process [20]. As shown in Fig.2 (a), incident light is scattered by the turbid medium (TM) and collected into a material with certain optical system. With a coherent reference beam *R*, a hologram can be recorded in the material. By illuminating the hologram with a conjugated reference beam *R**, a conjugated signal beam is reconstructed to compensate the distortion induced by scattering medium to the signal beam. Early demonstration on conventional holographic material-based OPC for imaging through TM was reported by Kogelnik [20], Goodman, et al.[4] and Leith et al.[3] independently.

In 2008, Yaqoob et. al. used a $LiNbO_3$ photorefractive crystal as recording material and demonstrate turbidity suppression in biological tissue at the first time[16]. McDowell et al. reported that OPC focus could be obtained even with only 0.02% portion of scattered light by applying this technique to 7 mm chicken tissue[21]. In 2010, Cui et al. extended this technique for in-vivo OPC by focusing through a living rabbit ear[22].

Compared to focusing through biological tissue, focusing light into it is more desired as the later technique has potential on practical applications in the field of biomedical imaging, manipulation and therapeutic. In 2011, Xu et al. proposed time-reversed ultrasonically encoded (TRUE) optical focusing in TM with $Bi_{12}SiO_{20}$ photorefractive crystal as PCM[13]. The observation of TRUE optical focusing in biological tissue up to 5-mm chicken tissue was then reported[23]. The principle of TRUE technique is schematically shown in Fig.2 (b). A focused ultrasonic wave modulates the frequency of scattered light in the TM. Although both ultrasound-tagged and untagged photons are coupled into PCM, only the interference pattern between the modulated signal beam and reference beam is recorded as they have the same frequency. Therefore, the retrieved conjugated signal beam recovers an optical focus that is composed of ultrasound-tagged photons in TM. The resolution of TRUE focus is determined by the focus of ultrasound and could be improved with two ultrasound transducers[24].

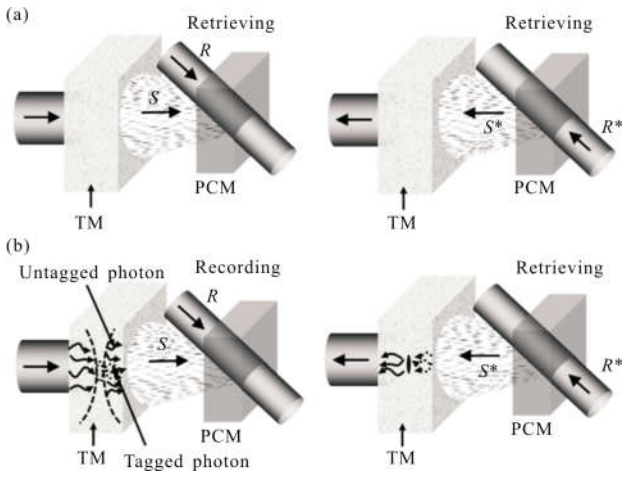

Fig.2 Schematic of holographic material-based OPC system for focusing through (a) and inside (b) TM

Three important parameters determine the efficacy of TRUE focusing in biological tissue, thus its application for biological application: focus-to-background ratio (FBR) or peak-to-background ratio (PBR), the speed of focusing and optical gain[25]. PBR is proportional to the number of controlled optical modes, but inversely proportional to the number of optical modes. The speed of TRUE focusing is especially important for in vivo biomedical application since the speckle correlation time of living tissue is usually in the order of milliseconds. TRUE technique would not form a focus if the time interval between recording and reading is much greater than the speckle correlation time. The optical gain characterizes the enhanced optical energy delivered in the conjugated signal beam compared to original ultrasonically

encoded light energy.

The speed of TRUE focusing is related to the response time of holographic material and light intensities for writing and reading holograms in the material. Typical recording time is 200 ms in BSO photorefractive crystal for TRUE focusing in thick biological tissue. In 2014, Liu et al. applied a fast-response holographic crystal for near-infrared TRUE focusing inside TM. The overall system time could be as fast as 5.6 ms and is capable for focusing inside dynamic TM[26].

To overcome the low energy conversion efficiency of TRUE technique with photorefractive crystal, a hybrid CW/pulsed holographic recording/reading system has been presented to provide 33 000 times power enhancement compared to conventional CW TRUE system[27]. 8 times energy enhancement was also demonstrated with a photorefractive polymer instead of BSO photorefractive crystal with the cost of longer system time[28]. A holographic fixing scheme was recently applied for focusing through TM to overcome instant erasure problem in photorefractive crystal[29], which is also possible for TRUE technique.

3 Digital holography-based OPC technique

Digital holography-based OPC method utilizes holographic interferometric technique to measure the phase of the scattered light and reconstructs the conjugated signal beam by reading out the uploaded phase pattern on a spatial light modulator (SLM)[30]. The schematic of typical digital OPC system is shown in Fig.3(a). The interference pattern of scattered signal beam and reference beam is captured by the camera. Then the phase of the signal beam could be calculated. When uploading the measured phase map on the SLM, the conjugated signal beam is obtained by illuminating a plane-wave similar to the reference beam. A precise alignment between pixels of the camera and SLM is required to perform high-quality focus for digital OPC. To overcome this time-consuming alignment procedure, several protocols were reported to not only decrease the calibration time but also improve the focal quality[31-33].

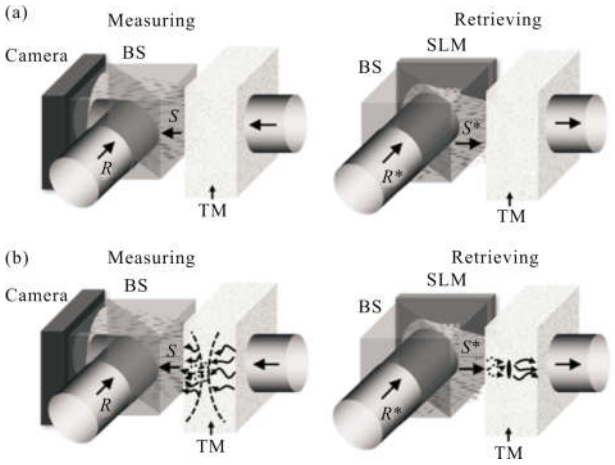

Fig.3 Schematic of digital holography-based OPC system for focusing through (a) and inside (b) TM

Compared to adaptive optics methods, DOPC has much more optical degrees of freedom, which leads to deep tissue applications[30-34]. Up to now, a penetration depth of nearly 100 transport mean free paths (TMFP) was achieved by focusing light through 9.6 cm tissue-mimicking phantoms and 2.5 cm chicken breast tissue[35]. Focusing through a highly scattering ex vivo adult human cataractous lens was also realized, which presents the potential clinical application of this technology[36]. However, it should be noted that the original DOPC system has response time of the order of hundreds of milliseconds[37], much longer than the correlation time of biological tissue with blood flow. This slow response is due to the limited speed of phase-only liquid crystal-based SLM and conventional computer data transfer. By using a high-speed digital mirror device(DMD) as SLM and field programmable gate array (FPGA) for data processing, the playback time of DOPC can be minimized to be 5.3 ms[38]. It is then capable to form a focus through 2.3 mm living mouse skin with flowing blood, which demonstrates the capability of DOPC for thick living biological tissue.

Similar as holographic material-based OPC technique, digital OPC system can also be extended for focusing into biological tissue with suitable guide star. By combining pulsed ultrasound modulation with digital OPC, Wang et al. and Si et al. independently demonstrated high optical gain($>10^3$) of digital system and implemented fluorescence imaging by digital TRUE optical focusing into biological tissue [39-40]. With SLM in digital system, phase pattern could exist within the speckle correction time of biological tissue, which overcomes the erasure problem in holographic material-based system. Fluorescence imaging with higher resolution was also realized by using iterative digital TRUE method[41-42] or time reversal of variance-encoded light (TROVE)[43].

Digital OPC method combining with other guide stars, such as nonlinear particles[44], fluorescence beads[45], microbubbles[46] or magnetic particles[47], were also explored for focusing inside biological tissue. Except the above methods with external/implemented guide stars, time-reversed adapted-perturbation (TRAP) optical focusing was developed using optical perturbation caused by moving absorbers as the internal guidestar [48-49]. TRAP focusing has higher perturbation efficiency than ultrasonic modulation-based schemes but could not be remotely controlled as ultrasound focus in TM. Among these methods, ultrasound offers the advantage of being noninvasive, deep penetration and freely addressable within the volume of interest. More recently, focusing on 2-mm-thick living brain tissue and its application for optogenetic modulation of neural activity in 800-μm thick acute mouse brain slices were demonstrated with digital TRUE technique[50].

4 Summary

OPC-based technique for focusing through/into TM is an important branch in the field of wavefront shaping. The final goal of this technique is to deliver optical energy for dynamic and opaque system, which would enable in vivo applications practical [51]. For imaging purpose, the PBR of the focus is also important for practical application. Generally, holographic material-based system could provide higher PBR than digital system due to more controllable modes ($>10^7$) than digital SLM. Although sub-Nyquist sampling [52] could improve the controlled modes by 1:1 pixel match between camera and SLM, the modes of digital method is limited by overall pixels (2×10^6) of current SLM[26]. More importantly, most of current digital system uses in-line holographic configuration that results in strong background from undiffracted reading beam. Off-axis holography is possible to increase the response speed of digital OPC but sacrifices the number of controllable modes[53].

As to the speed of OPC for focusing through/into TM, the response time of material could be less than millisecond [54] while the digital device has tradeoff between the speed and the amount of controlled modes. Fast SLM[55-56], lock-in camera[57], single exposure method[53,58], and programmable electronic device[38] could accelerate the digital OPC system but at the cost of other OPC performance. In principle, dynamic OPC light-field generation methods, such as four-wave mixing[9] or an electronic device combining camera and SLM are more desired than current static holography-based OPC. With these methods, the time delay between recording and playback is minimized so that the effect of movements and fluid flowing in living tissue is effectively nullified. It might be possible to suppress turbidity for thick living tissue with the advancement of holographic material and digital devices in the future.

Another important criterion for realistic application of above OPC systems is the attainable optical gain especially energy gain, which characterizes the delivered optical energy in the phase conjugated light relative to the original incident light energy. It is usually less than unity in current holographic material-based systems due to erase of the hologram. Digital systems could provide high energy gain but at the cost

of longer exposure time. It is necessary to explore holographic material for higher energy conversion or digital device that could provide both high energy gain and speed.

Overall, current development of OPC approaches for focusing through/inside TM shows a great potential for optical imaging, manipulation and therapy applications at depths in living biological tissue. With its ability of suppressing distortion for optical system, many imaging techniques, such as microscope, ultrasound optical tomography and so on, has integrated OPC in the system for deep tissue imaging. By delivering optical energy into thick tissue, various light-matter interaction like Raman, fluorescence, or non-linear optical interaction might be realized under the surface of biological tissue. Then it is also possible to control small particles with delivered optical energy or make changes to them. To pursue those promising and practical applications, more powerful holographic material and advanced digital devices are needed for further development of the above systems. Moreover, there are also needs to explore new biocompatible guide star with high tagging efficiency to improve the performance of focusing inside TM. It is then expected to see more exciting biological applications with further development of OPC-based approaches over the next several years.

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