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Application Exploration of the Photon Chip Technology in Real time Processing of Biomedical Images

Mingyu Sui

School of China Jiliang University, ZheJiang, China

ABSTRACT

In the biomedical field, photonic chip technology is gradually becoming the key to improving the speed and accuracy of medical imaging. The development of this technology has given us new hope in early disease diagnosis and cell monitoring. Recent research has not only sorted out the hotspots and future trends of biomedical photonics, but also paid special attention to the application of photon technology in these fields. Specifically, photonic chips have demonstrated their unique capabilities in multi-color two-photon excitation fluorescence microscopy imaging, two-photon fluorescence lifetime imaging, and two-photon fiber endoscopic imaging. These applications not only improve the clarity of imaging, but also accelerate processing speed, which is crucial for rapid diagnosis and treatment. At the end of the article, the author summarized the contributions of photonic chip technology in the field of biomedical imaging and provided prospects for future development directions.

KEYWORDS

Photon chip; Real time processing; Biomedical images

1. INTRODUCTION

With the rapid development of technology, biomedical research is becoming increasingly refined and focusing more on real-time performance.

In this process, image processing technology is really crucial, especially in the diagnosis and treatment of diseases. But to be honest, traditional image processing methods are still lagging behind in speed and accuracy, and cannot keep up with the high requirements of modern medicine for high-definition and real-time imaging.

Fortunately, the emergence of photonic chip technology is like a clear stream, bringing revolutionary changes to biomedical image processing with its ultra-fast processing speed, low energy consumption, and high integration. This article aims to discuss the photonic chip technology and see what it can do in real-time processing of biomedical images, as well as what possibilities it has in the future.

The widespread application of this technology not only takes biomedical imaging technology a big step forward, but also provides new ideas and methods for personalized medicine and precision treatment, which is definitely worth our in-depth research.

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2. BIOMEDICAL AND PHOTONICS

2.1. Origin, Development and Future

Biology or life sciences are an important application field of photonics. In the 21st century, all science and technology will revolve around the issue of human development, seeking their own meaning and direction of existence. The most peculiar and ever-changing phenomenon of life in nature, from its origin and evolution to today's human behavioral abilities and potentials, is closely related and inseparable from the mysterious substance of light. Light and life have already formed an inseparable bond. Over the past decade, the sudden rise of biomedical optics and photonics has attracted widespread attention, giving rise to a new discipline - biomedical photonics. In short, biomedical photonics is the science of using photons to study life. It is an interdisciplinary field that arises from the intersection and permeation of photonics and life sciences.

Now, the combined application of laser technology and photoexcited drugs can even treat certain cancers. The mobile blood cell meter based on optical diagnostic technology can be used to monitor the amount of virus carried by AIDS patients. Some optical technologies are in the experimental stage of non-destructive medical applications, including non-destructive blood glucose monitoring for diabetes control and early diagnosis of breast cancer. Biomedical photonics has become one of the important development directions of international optics disciplines and occupies an important position in the field of biomedical engineering. In the future, the focus of development in the field of optics is to apply various complex optical systems and technologies more widely to healthcare and medical care, including the development plan for third-generation autonomous platforms for air sampling and virus molecule analysis for haze detection. Biomedical photonics technology based on modern laser and optoelectronic technology is expected to bring original and important achievements to life science research, and is expected to form an industry with significant social impact and economic benefits.

2.2. Research Focus

Biomedical photonics involves the energy released by biological systems in the form of photons, the process of detecting photons from biological systems, and the structural and functional information carried by these photons about biological systems. It also includes the processing and modification of biological systems using photons. In other words, the optics and related application technologies involved in biological research, medical research, diagnosis, and treatment, including the most fundamental photophysical problems, are all research objects of biomedical photonics. The research in this field not only covers the interaction between light and biological systems, but also includes the application technology of photons in biomedicine, providing new perspectives and methods for the study of life sciences.

In the past thirty years, with the development of lasers and new photon technologies, biomedical photonics has entered a rapidly developing new stage. The advancement of optical related technologies is impacting the field of human health, changing the implementation methods of drug therapy and conventional surgery, and bringing revolutionary new methods to medical diagnosis. These technologies have been studied in early disease diagnosis, physiological parameter monitoring, gene expression, protein-protein interactions, new drug development, and efficacy evaluation. In the field of ophthalmology, optical and laser technologies have been skillfully applied in clinical practice. In addition, laser technology has achieved new therapies in the treatment of kidney stones and skin diseases, and has replaced certain surgical procedures, such as knee joint repair surgery, with non-destructive or minimally invasive therapies.

3. APPLICATIONS OF PHOTON CHIP TECHNOLOGY IN REAL TIME PROCESSING OF BIOMEDICAL IMAGES

3.1. Fluorescence Microscopy Imaging of Multicolor Two-Photon Excitation

Monitoring the dynamic characteristics and interactions of cells, proteins, DNA, and other components in the human microenvironment is of great significance for in vivo imaging and immunotherapy research. Multi color fluorescence microscopy imaging uses fluorescent groups with different emission spectra to label different cells, proteins, DNA, etc. By distinguishing the type and function of labeled samples through the spectral information of fluorescent groups, dynamic tracking of multiple markers can be achieved. In confocal imaging, single photon multi-color imaging usually uses one wavelength to excite multiple markers. However, due to the narrow single photon excitation spectrum of fluorescent groups, the excitation spectra of different fluorescent groups may vary greatly, making it difficult to excite multiple fluorescent groups at one wavelength. Figure 1 shows a typical laser scanning multi-color two-photon excitation fluorescence microscopy imaging system.

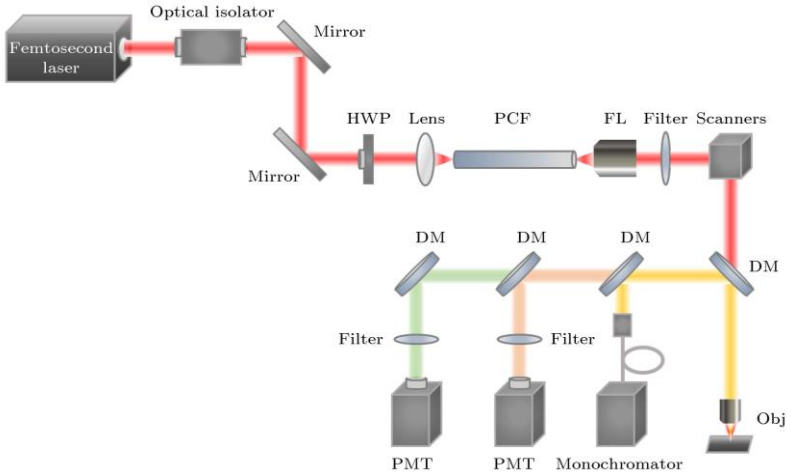

Figure 1. Schematic diagram of laser scanning multi-color two-photon excitation fluorescence microscope system

For real-time dynamic monitoring of multi-color labeled fluorescent groups, it is necessary to simultaneously and effectively excite multi-color fluorescent markers, and quickly distinguish the cells, organelles, or proteins labeled by the fluorescent markers during imaging. Due to the wider two-photon absorption spectra and higher spectral overlap of many fluorescent substances compared to single photon absorption spectra, a single wavelength light source can also excite multiple fluorescent groups simultaneously, achieving multi-color two-photon excitation fluorescence microscopy imaging. However, the optimal excitation wavelength for fluorescent groups is often inconsistent, and a single wavelength light source cannot achieve optimal excitation. Moreover, when the two-photon absorption cross-section of the fluorescent group itself is small, in order to obtain fluorescence signals from multiple fluorescent groups, it is often necessary to increase power to improve fluorescence intensity, which can cause phototoxicity and photobleaching effects. In addition, increasing laser power can also induce endogenous spontaneous fluorescence in cells, which may have spectral overlap with the fluorescence emitted by the fluorophore used. This spectral crosstalk can affect the dynamic monitoring of labeled cells or proteins.

In order to achieve optimal excitation of multiple fluorescent groups simultaneously and improve the signal intensity of multi-color two-photon excitation fluorescence microscopy imaging, multiple wavelength or broadband spectral excitation light sources can be used. The implementation of the former method can use two or more femtosecond lasers as multi wavelength excitation light sources, or use methods that expand the spectral band of excitation light, such as optical parametric oscillators. By using a titanium sapphire oscillator as a pump source, OPO can output continuously tuned ultra

short pulse lasers in the near-infrared wavelength range above 1200nm. However, the cost of increasing the light source is high, and the imaging path becomes complex as a result, which limits the application of this multi excitation source technology in multi-color two-photon excitation fluorescence microscopy imaging. The latter method utilizes broadband compressible continuous spectral pulses to achieve multi-color two-photon excitation fluorescence microscopy imaging, mainly including two types: broadband pulses emitted by sub-20fs lasers and fiber continuous spectra generated by 100fs lasers. The short pulses generated by the sub-20fs laser have a phase stable spectral bandwidth of over 100nm. The phase function introduced by pulse shaping changes the phase coherence of the pulse spectrum, thereby altering the pulse frequency and further enhancing the two-photon excitation efficiency of the fluorophore, achieving selective excitation of the corresponding fluorophore. This method does not require adjusting the optical path to select the excitation wavelength, but the system is equally complex and requires a specific laser. The use of optical fibers to generate supercontinuum light for multi-color two-photon excitation fluorescence microscopy imaging only requires the commonly used 100fs laser. The principle is to utilize the nonlinear transmission characteristics of femtosecond pulses in the fiber, combined with pulse compression technology to generate broadband spectra and short pulse width femtosecond pulses. This technology can not only achieve optimal excitation of multi-color two-photon fluorophores, but also significantly improve the efficiency of two-photon excitation fluorescence. Early continuous spectroscopy was generated by laser transmission in the normal dispersion region of ordinary single-mode fibers, but the light source system was very complex. Currently, people use photonic crystal fibers with zero dispersion points to generate continuous spectra. The soliton effect can generate a wide spectral range of continuous spectra, and selecting appropriate PCF parameters can effectively control the position of the zero-dispersion point. However, due to the soliton effect usually occurring in the anomalous dispersion region of PCF, the continuous spectrum it produces is highly sensitive to vibration and noise. Even very weak vibrations can cause significant changes in the spectral structure, leading to a drastic decrease in spectral coherence. Therefore, designing simpler systems to achieve simultaneous optimal wavelength excitation of multiple fluorescent groups while ensuring two-photon excitation efficiency and avoiding spectral crosstalk issues to a certain extent remains an important direction for the development of multi-color two-photon excitation fluorescence microscopy imaging technology.

Garaschuk et al. injected a mixture of various dyes into the mouse brain and performed multi-color imaging to obtain images of different neurons and glial cells at 500 μ m on the surface of the mouse brain. This method is suitable for staining brain tissues at different developmental stages of different species and can also record real-time calcium signals in vivo. Mahou et al. utilized a femtosecond laser and synchronous pulses generated by OPO to achieve multi-color two-photon excitation fluorescence microscopy imaging of three fluorophores with different absorption spectra. Real time multi-color imaging of mouse brain tissue and multi-color fluorescence and third harmonic imaging of fruit fly embryos were achieved by using fluorescent groups to label cells. In 2014, Mahou et al. extended their previous work by combining two-photon illumination with mixed wavelength excitation to achieve four-dimensional multi-color fluorescence microscopy imaging of beating hearts in zebrafish embryos at a pixel rate of 28MHz, with almost negligible photobleaching. In 2017, the team utilized wavelength mixing technology to achieve efficient dual color two-photon imaging of NADH and FAD, two endogenous fluorescent groups. At the same time, they combined two-photon excitation fluorescence lifetime imaging technology to reconstruct the lifetime gradients of NADH and FAD in human skin and nematodes. Subsequently, in 2019, the team proposed the Chromatic Multiphoton Serial Microscopy (ChromS), which combines three color two-photon excitation with automatic continuous tissue sectioning through wavelength mixing technology, achieving multi-color imaging with micrometer level resolution. As a result, three-dimensional multi-color imaging of the mouse brain was also achieved. Figure 2 shows the results of three-dimensional multicolor imaging of mouse cortical tissue.

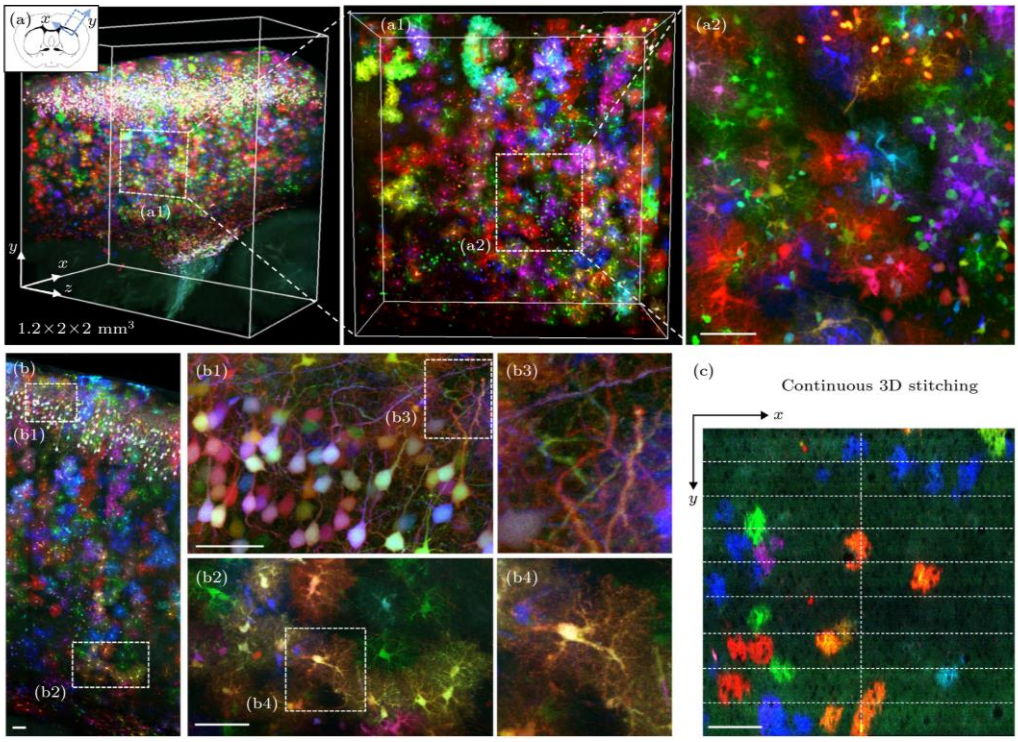

Figure 2. Continuous three-dimensional multicolor imaging of mouse cortical tissue

3.2. Lifetime Imaging of Two Photon Excitation Fluorescence

Fluorescence lifetime refers to the average residence time of the molecules that make up a substance in the excited state after being excited by a light pulse and transitioning to a high energy level, before returning to the ground state. It is approximately in the order of ns and is commonly represented by τ. The fluorescence lifetime is an inherent property of fluorescent substances, usually independent of factors such as laser excitation intensity, illumination time, and dye concentration, but related to the microenvironment and structure of the substance itself. Due to the inherent nature of fluorescent molecules, FLIM technology can provide fluorescent dye labeling that is clearer than intensity and spectrum, and it contains information about the local molecular environment and chromophore photophysical properties of fluorescent labeling. Therefore, FLIM technology has the advantages of strong specificity and high sensitivity in imaging, which can enhance the image contrast of biological samples and also obtain physical, chemical, and biological information in the microenvironment where fluorescent molecules are located. This technology has become a powerful tool for studying the biochemical properties of samples in the fields of biology, biophysics, and life sciences.

They found that injecting sub micromoles of A β into the slices significantly increased the Ca^{2+}concentration in adjacent astrocytes, reflecting the physiological effects of A β on brain cells. Afterwards, the team used two-photon FLIM technology to image the calcium ion fluorescent indicator OGB-1 and developed a method for monitoring intracellular Ca^{2+}ions in single cells. This method was demonstrated to have higher signal-to-noise ratio and sensitivity on brain slices and in situ nerve cells. Feeks et al. combined adaptive optics with two-photon FLIM to image non intrinsic fluorescent groups in the mouse retina. By using genetically encoded calcium indicators in a mouse model, changes in two-photon spontaneous fluorescence and fluorescence lifetime were observed, allowing for the detection of various functional responses. This research also opens the door for further application of molecular targeting and research on disease progress. By observing the changes of retinal fluorescence life span, we can detect disease progress for patients with diabetes retinopathy and Stagat disease at an earlier stage. Parkinson's disease is currently one of the most troubling diseases for humans.

Chakraborty et al. used two-photon FLIM to study the fluorescence lifetime components of NADH and FAD in neuronal cells, as well as the changes in lifetime after MPP+(1-methyl-4-phenylpyridine) treatment. The team found that in cells treated with MPP+, there was a statistically significant decrease in the fluorescence lifetime of NADH and FAD of free and bound proteins. These results indicate a shift in energy production from oxidative phosphorylation to anaerobic glycolysis in cells treated with MPP+, which could potentially be used as a cellular metabolic indicator to assess Parkinson's disease at the cellular level.

3.3. Fiber Endoscopic Imaging of Two Photon

Although traditional 2PEF can provide us with clear imaging of biological cell tissues, due to its complex imaging system, numerous devices, and large size. And at present, most imaging of biological cell tissues is still limited to in vitro cell culture or to a certain depth on the surface of the organism. The microenvironment inside living organisms is truly intricate and complex. The simulated environment in the laboratory is vastly different from the real environment inside living organisms. Sometimes, the phenomena you observe in the laboratory may be completely different when placed in living organisms.

Although methods such as abdominal window surgery can achieve cellular tissue imaging in vivo, these methods are highly invasive, cause significant damage to the organism, and cannot achieve long-term in vivo imaging. These factors limit the application of two-photon microscopy in in in vivo imaging.

The two-photon fiber optic endoscopy technology also plays an important role in clinical diagnosis and treatment. In 2012, the Louradour team proposed a nonlinear fiber spectrometer with adjustable excitation wavelength, with a wavelength adjustment range of 700-900nm and a pulse width of 70fs. It can perform nonlinear spectral analysis on isolated human lung tissue through two-photon signals of elastin and SHG signals of collagen.

Two challenges will be faced when using two-photon fiber optic endoscopy technology. Firstly, the two-photon absorption of most endogenous fluorescent groups in organisms is located in the optical window of 700-900nm, where the fiber has significant dispersion; Secondly, the nonlinear self-phase modulation (SPM) effect can widen the frequency spectrum of the excitation signal, leading to signal distortion. The team compensated for the nonlinear effects of spectral compression by introducing a standard polarization maintaining single mode fiber (PM-SMF) and using pulse extenders to compensate for second-order and third-order dispersion, ensuring that the system can transmit infrared excitation pulses of less than 40fs at the output end of a 5m long fiber. In addition, by designing a customized pure silica core DC-PCF, high spatial resolution can be ensured, and the performance of femtosecond pulses in fiber transmission can be guaranteed without polarization mode dispersion caused by bending. At the output end of the endoscope, the team used a resonant fiber scanner and micro-optics (MO) to build a small imaging probe with an outer diameter controlled at 2.2mm. In 2015, the team designed a two-photon fiber endoscope based on DC-PCF with a size of only 2.2mm, which can simultaneously detect two-photon and SHG signals at a speed of 8 frames per second. The lateral and axial resolutions are 0.8 μ m and 12 μ m, respectively, and the maximum imaging field of view is 450 μ m × 450 μ m. The imaging penetration depth can reach 300 μ m below the organ surface, making it a powerful tool for real-time pathological assessment in clinical practice. When a power of 5mW is applied to the sample, the system can image the sample with high sensitivity of 8 frames per second. By adjusting the input half wave plate, different orthogonal linear polarizations can be selected. When the excitation polarization is parallel to collagen, a stronger SHG signal can be obtained.

4. CONCLUSION

This paper explores the application of photonic chip technology in real-time processing of biomedical images. By analyzing the existing fields and development directions of biomedical photonics, the important role of photonic chip technology in multi-color two-photon excitation fluorescence microscopy imaging, two-photon excitation fluorescence lifetime imaging, and two-photon fiber optic endoscopic imaging is demonstrated. Photon chip technology, with its efficient and precise photon processing capabilities, provides strong support for biomedical image processing, effectively improving image clarity and real-time performance. With the further development of fiber optic endoscopy technology and multiphoton imaging technology, photonic chips are expected to have greater potential in clinical diagnosis, disease monitoring, and personalized medicine. Future research should continue to focus on optimizing chip performance and improving application efficiency to promote innovation and progress in biomedical imaging technology.

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