Plenary Presentations

[PL-1]

Britton Chance, PIBM and the Luo Lab

Qingming Luo[1,2]

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Abstract: PIBM is the largest international series conference in biomedical photonics hosted in Asia. Suggested by Dr. Britton Chance, father of biophotonics, PIBM was launched by Huazhong University of Science and Technology biyearly in 1999-2005 and became yearly in 2006-2014. PIBM is designed as a forum where scientists, engineers, and clinical researchers from multidisciplinary fields communicate to apply optical and imaging solutions to answer the questions in biology and medicine. The scope of this conference ranges from basic research to application and demonstration, including but not limited to neurophotonics, immunophotonics, agri-photonics, analytical biophotonics, and translational biophotonics.

In this talk, I will introduce my late mentor, Dr. Britton Chance's contribution to PIBM, and the biomedical photonics research in my lab since 1997.

Qingming Luo
Professor
Hainan University, China

Dr. Luo is the President of Hainan University, President-Elect of the Chinese Society of Biomedical Engineering (CSBME), and Chair of the MoE Steering Committee for Biomedical Engineering Teaching in Colleges and Universities. His research interests focus on multi-scale optical bioimaging and cross-level information integration. He is an elected Member of the Chinese Academy of Sciences (CAS) and the Chinese Academy of Medical Sciences (CAMS), an elected Fellow of The International Academy of Medical and Biological Engineering (IAMBE), American Institute for Medical and Biological Engineering (AIMBE), Optica (formerly OSA), Institution of Engineering and Technology (IET), International Society for Optics and Photonics (SPIE) and Chinese Optical Society (COS).

[PL-2] PIBM2024-0811-1

Activatable Photosensitizers: from Single Molecules to Nanoparticles and Beyond

Gang Zheng

University of Toronto and Princess Margaret Cancer Centre, Canada

Abstract: Photodynamic therapy (PDT) is a therapeutic modality in which a light-absorbing drug called a photosensitizer is combined with light and molecular oxygen to generate cytotoxic singlet oxygen. In 2004, my lab introduced the concept of activatable photosensitizers, which allows the photosensitizer's ability to generate singlet oxygen to be silenced until a disease-specific linker-target interaction takes place. Thus, this new class of PDT agents can achieve a very high level of disease treatment selectivity by destroying only the targeted cells, while leaving non-targeted cells unharmed. In 2011, while pursuing a nanoparticle-based activatable photosensitizer, we discovered porphysomes, the liposome-like nanoparticles self-assembled from a single porphyrin-lipid building block. High-density porphyrin packing in its bilayer enables light absorption and conversion to heat with extremely high efficiency, making porphysomes ideal candidates for photothermal therapy and photoacoustic imaging. Upon nanostructure dissociation during cell uptake, the fluorescence and PDT activity of the porphyrin monomers is restored. In addition, metal ions can be directly incorporated into the porphyrin building blocks, thus unlocking porphysome's potential for PET, MRI and radionuclide therapy. The porphysome has trod a path towards the clinic for the past ten years and is now ready for its first-in-human use, aka 'beyond lab'. We have also developed a suite of next generation porphysomes that greatly broadened its theranostic applications from light to sound to radiation to immunomodulation. These allow us to pursue new directions of 'beyond light', 'beyond local', and 'beyond cancer'.

Gang Zheng
Professor
University of Toronto and Princess Margaret Cancer Centre, Canada

Dr. Gang Zheng is an Associate Research Director of the Princess Margaret Cancer Center. He is also a Professor and Tier 1 Canada Research Chair in Cancer Nanomedicine at the University of Toronto. He obtained his BSc in 1988 from Hangzhou University and PhD in 1999 from SUNY Buffalo. Following a postdoctoral training in photodynamic therapy at the Roswell Park Cancer Institute, he joined the University of Pennsylvania in 2001 as an Assistant Professor of Radiology and moved to Canada in 2006. His lab is best known for introducing the activatable photosensitizers for photodynamic therapy and the porphysome nanotechnology for cancer theranostics. Dr. Zheng is a Fellow of the American Institute of Medical and Biological Engineering and an Associate Editor for Bioconjugate Chemistry.

[PL-3]

Dynamics of proteins post structural age

Dongping Zhong

Shanghai Jiao Tong University, China

Abstract: We have witnessed the big success on solving protein structures by the recent Nobel prize in chemistry. But their dynamics and mechanisms have been challenging due to the complexity and lack of the tools. Here, we overview the current efforts and present our studies on protein dynamics using ultrafast femtosecond spectroscopy, including recently developed XFEL and ultrafast electron microscopy. A few examples are the entire repair dynamics of damaged DNA, photoreceptor dimer dissociation, and optical quantum control of protein electorn transfer.

Dongping Zhong
Professor
Shanghai Jiao Tong University, China

Dongping Zhong currently is the Chair Professor in Shanghai Jiao Tiong University. He received his Ph.D. in chemical physics from Caltech in 1999 under the late Prof. Ahmed H. Zewail. For his Ph.D. work, Dr. Zhong received the Milton and Francis Clauser Doctoral Prize from Caltech. In 2002, he joined The Ohio State University and was promptly promoted as Robert Smith Professor of Physics and Professor of Chemistry and Biochemistry. He is the Packard Fellow, Sloan Fellow, Camille Dreyfus Teacher-Scholar, Guggenheim Fellow, APS Fellow, AAAS Fellow, as well as the recipient of the NSF CAREER award. His early work on femtochemistry and recent work on the dynamics of enzyme catalysis have been cited in the press release and Noble lecture of two Nobel Prizes (1999 and 2015).

[PL-4] PIBM2024-0731-7

Development of localized ablative immunotherapy from benchtop to bedsite

Wei R. Chen

Stephenson School of Biomedical Engineering, University of Oklahoma, USA

Abstract: The biggest challenge for cancer treatment is metastasis, due to the failure of the host immune system in detecting and destroying cancer cells, particularly the metastatic tumor cells. In fact, 90% of cancer deaths are caused by metastasis. Unfortunately, we have limited options in treating metastatic cancers. Because of the immunological root cause of cancer, the potential solution should be immunotherapy to activate, enhance, and direct the host immune system to systemically eradicate cancer and prevent cancer recurrence. However, the current immunotherapies have limitations. Because the ubiquitous antigens for any given tumor have not been found, no effective tumor vaccine is available. Using immunoadjuvant and immunostimulant alone lacks tumor specificity. Even advanced immunotherapy, such as immune checkpoint blockade only has low patient response rate, about 10 to 30%. To overcome these limitations, particularly to address the challenges posed by metastatic tumors, which are often not detectable or treatable, we developed the localized ablative immunotherapy (LAIT). It is a combination of targeted ablation therapy and immunotherapy, using local intervention to induce systemic immune responses to treat metastatic tumors. In this talk, I will first introduce our unique modality. Then, the treatment procedure and mechanism of action and the MOA at transcriptomic level. Then, I will focus on the clinical results using LAIT. Finally, I will report the current status and future direction of LAIT.

Wei R. Chen
Professor
University of Oklahoma, USA

Dr. Wei R. Chen received his BS degree in physics from Shandong University, Jinan, China, in 1982. He received his PhD degree in theoretical high-energy particle physics from the University of Oregon in 1988. He changed his research from physics to cancer research in early 1990s. Currently, he is Stephenson Chair and Professor, and the Interim Director of the Stephenson School of Biomedical Engineering at the University of Oklahoma. Dr. Chen is a pioneer in the field of immunophotonics. His group developed localized ablative immunotherapy for metastatic cancers using the combination of local laser ablation and local administration of a novel immunostimulant, with promising outcomes in pre-clinical studies and preliminary clinical trials. He has published 180+ peer-reviewed articles (with an h-index of 59). He has been awarded 11 US patents and multiple international patents. Dr. Chen has received more than $10 million in funding from state and federal agencies, foundations, as well as from industrial sponsors. He was elected as a SPIE (International Society of Optics and Photonics) Fellow in 2007, and an AIMBE (American Institute for Medical and Biomedical Engineering) Fellow in 2022. He received the 2008 US Professor of the Year award and the 2011-2012 US Fulbright Lecturing/Research Award. He also won the Medal for Excellence in Teaching from the Oklahoma Foundation for Excellence in 2011 and the SPIE Educator Award in 2012. Dr. Chen is a co-founder and a board director of Immunophotonics, Inc. The company has received the US FDA approval in April 2023 for a phase 1b/2a multicenter clinical trial for patients with late-stage colorectal cancer, non-small cell lung cancer, and soft-tissue sarcoma, using the novel therapy developed by Dr. Chen's team.

[PL-5] PIBM2024-0820-1

Morphological and functional characteristics of Adriamycin-induced chronic kidney disease (CKD) based on two-photon microscopy *in vivo*

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Abstract: Kidney disease refers to a group of chronic and naturally occurring heterogeneous diseases that impact kidney structure and result in decreased renal function. Adriamycin, a drug known to induce renal insufficiency, serves as an effective approach to induce a murine model of chronic kidney disease (CKD) for studying homeostasis, drug toxicity, and renal transplantation. In our study, intravital two-photon microscopy (TPM) were employed to investigate the kidney's morphological and functional characteristics in an adriamycin-associated rat CKD model *in vivo*. Morphological changes in renal tubules were analyzed using autofluorescence images at various time points after adriamycin injection. High-molecular-weight (MW) 500-kDa dextran-fluorescein and low-molecular-weight (MW) 10-kDa dextran-Rhodamine were used to investigate the functional properties of kidney, including blood flow, glomerular filtration rate, and permeability. The results demonstrated that prolonged time post Adriamycin-injection led to noticeable changes in kidney morphology and biochemical indexes, and gradual deterioration of functional characteristics. These parameters hold potential as indicators for evaluating CKD. The combined analysis of these parameters may offer a novel quantitative method for monitoring CKD and assessing the therapeutic effects of drugs.

Yu Chen
Professor
Fujian Normal University, China

Dr. Yu Chen received his BS from Peking University in 1997 and his PhD from the University of Pennsylvania in 2003. After postdoctoral training at MIT, he joined the University of Maryland (College Park) in 2007 as an Assistant Professor, and was promoted to Associate Professor in 2014. He moved to the University of Massachusetts (Amherst) in 2019, and was promoted to Professor in 2023. He is currently a Professor at the Fujian Normal University, China, and serves as the Interim Director of the Minister of Education Key Laboratory of Optoelectronic Science and Technology for Medicine. Dr. Chen has published over 110 peer-reviewed journal publications. He received the National Science Foundation CAREER Award. He is an associate editor of Biomedical Optics Express. His research is focused on the development of optical techniques for biomedical applications including cancer detection and transplant organ evaluation.

[PL-6]

Tissue optical clearing: new approaches towards *in vivo* applications

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Abstract: Tissue optical clearing (TOC) is based on the temporary and reversible suppression of tissue light scattering using biocompatible immersion optical clearing agents (OCAs) [1-6]. Delivery of the appropriate OCA into living tissue ensures its transient transparency over a wide spectral range from deep UV to NIR and further to THz, providing higher imaging depth and contrast for a variety of optical modalities, including single- and multiphoton fluorescence, harmonic generation (SHG, THG) microscopy, OCT, Raman, photoacoustics (PA), etc.

The presentation summarizes the latest advances in the development of the TOC method for solving problems of intravital optical imaging and diagnostics. In addition to increasing optical transparency, studying the kinetic properties of tissue transparency under the influence of OCA probe molecules makes it possible to reliably differentiate between healthy and pathological tissues and quantify drug delivery mechanisms, as well as combine optical technologies with traditional imaging methods such as ultrasound, CT and MRI.

Benefits of the method: 1) Tissue optical clearing technology is useful for advanced multimodal spectroscopy/imaging and light therapy. 2) The efficiency of biomedical optical spectroscopy/imaging techniques operating over a wide range of wavelengths from the deep UV to the THz range is improved significantly. 3) The combination of optical techniques such as Raman, OCT, FLIM, MPM, SHG, PA, diffuse reflectance and THz with X-ray CT and MRI is possible through the use of FDA approved commercial contrast agents. 4) The optical clearing method provides additional markers for monitoring *diabetes mellitus* complications and cancer detection. 5) The technique provides important data for optimal cryopreservation of organs.

This work was supported by RSF grant No. 24-44-00082 "Development of optical methods for studying glycation and hemodynamics of biological tissues in diabetes mellitus"

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Valery V. Tuchin
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Valery V. Tuchin is the corresponding member of the Russian Academy of Sciences, Head of the Department of Optics and Biophotonics and Director of the Science Medical Center at Saratov State University. He is also works with several other research centers of the RAS and universities. His research interests include biophotonics, biomedical optics, and nanobiophotonics. He is the Honored Scientist of Russia, Fellow of SPIE and OPTICA, Distinguished Professor of Finland, recipient of SPIE Educator Award, Joseph W. Goodman Book Writing Award (OPTICA/SPIE), Michael S. Feld Biophotonics Award (OPTICA), Chime Bell Award of the Hubei, the D.S. Rozhdestvensky Medal and the S.I. Vavilov Medal of the Russian Optical Society, and the A.M. Prokhorov Medal of the Russian Academy of Engineering Sciences. His publications have been cited over 42000 times.

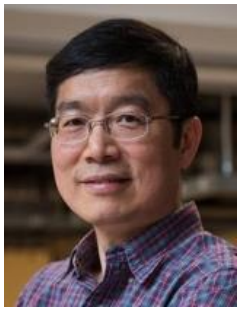
[PL-7]

Photoacoustic, Light-Speed, and Quantum Imaging

Lihong V. Wang

Caltech, USA

Abstract: We developed photoacoustic tomography (PAT) for deep-tissue imaging, offering in vivo functional, metabolic, molecular, and histologic imaging from organelles to entire organisms. PAT combines optical and ultrasonic waves, overcoming the optical diffusion limit (~1 mm) with centimeter-scale deep penetration, high ultrasonic resolution, and optical contrast. Applications include early cancer detection and brain imaging.
Additionally, we developed light-speed compressed ultrafast photography (CUP), capable of capturing the fastest phenomena, such as light propagation, in real time. CUP, with a single exposure, captures transient events on femtosecond scales. CUP can be paired with various front optics, from microscopes to telescopes, facilitating diverse applications in fundamental and applied sciences, including biology and cosmophysics.
Further, our research extends to quantum entanglement for imaging. Quantum imaging utilizing Heisenberg scaling enhances spatial resolution linearly with the number of quanta, outperforming the standard quantum scaling's square-root improvement.



Lihong V. Wang
Ph.D.
California Institute of Technology, USA

Lihong Wang is Bren Professor of Medical and Electrical Engineering at Caltech. Published 605 journal articles (h-index = 162, citations = 112,000, #1 most cited scientist in optics according to Stanford/Elsevier). Delivered 620 keynote/plenary/invited talks. Published the first functional photoacoustic CT, 3D photoacoustic microscopy, and light-speed compressed ultrafast photography (world's fastest camera). Served as Editor-in-Chief of the Journal of Biomedical Optics. Received the Goodman Book Award; NIH Outstanding Investigator, NIH Director's Transformative Research, and NIH Director's Pioneer Awards; Optica Mees Medal; IEEE Technical Achievement and Biomedical Engineering Awards; SPIE Chance Award; IPPA Senior Prize; Optica Feld Award; an honorary doctorate from Lund University, Sweden. Inducted into the National Academy of Engineering.

Keynote Presentation

[AK-1] PIBM2024-0926-1

Photodynamics of molecular probes in solutions, cells and on organic surfaces

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Abstract: The lecture presents the review of recent studied that have been carried out in the Ioffe Institute, Russian Academy of Sciences in the field of photodynamics of photoseensitizers (PS) and biomolecules in solutions, living cells, and on organic surfaces by means of time-resolved fluorescence polarization spectroscopy and fluorescence lifetime imaging microscopy (FLIM). Detailed investigations of the fluorescence of coenzymes NADH and FAD in water-alcohol mixtures (methanol, ethanol, propylene glycol) and of a photosensitizer Chlorin e6 that are now widely used for photodynamics therapy of oncology diseases and for photodynamic purification of organic surfaces have been carried out. A significant increase of fluorescence quantum yield in NADH and FAD with increase of alcohol concentration was observed. A new model has been developed for elucidation of the effect observed that takes into consideration several possible energy transfer channels in the coenzyme excited states after excitation with ultrashort laser pulses. The mechanisms of these relaxation processes were analyzed for each type of coenzymes under study. The investigation of PS Chlorin e6 distribution with FLIM in living cells and for the mapping of pH distribution inside cells. A new effective method of singlet oxygen generation on organic surfaces has been developed. The method is based on the excitation of a PS dissolved in an appropriate solution and pulverized on the surface by a gas spay. Singlet oxygen generation quantum yield and PS Chlorin e6 photobleaching on various organic and non-organic surfaces were under study. An intriguing decrease by several decades of the photobleaching rate of PS on organic surfaces with respect to non-organic surfaces has been observed. The investigation of the photobleaching rate allowed for understanding of the photobleaching mechanism. As was shown, the PS photobleaching on organic surfaces occurred mainly due to interaction with oxygen molecules.

Oleg S. Vasyutinskii
Professor
Ioffe Institute, Russia

1997 Visiting Professor, Institute for Molecular Sciences, Okazaki, Japan (with Prof. Toshinori Suzuki)
2001 Visiting Professor, Alexander von Humboldt Research Award, TU Berlin (with Prof. Dieter Zimmermann), TU Braunschweig (with Prof. Karl-Heinz Gericke), Germany
2004-2015 Adjunct Professor, Wayne State University, Chemical Department, Detroit, MI, USA (with Prof. Arthur G. Suits)
2005-2009 DAAD Visiting Professor, TU Braunschweig, Germany.
2009-till now: Professor, Polytechnic University, St.Petersburg
2010-till now: Professor, Academic University, St.Petersburg
Now: Head of the Laboratory "Optics of Biomolecules and Clusters", Ioffe Institute, St.- Petersburg, Russia.

Invited Presentations

Analytical Biophotonics

[AI-1] PIBM2024-0912-1

Terahertz nanoscopy of single proteins

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Abstract: Terahertz (THz) technology has attracted increasing interest worldwide. In the past years, much progress has been made in THz biomedical research. However, the low spatial resolution of conventional THz techniques has seriously hampered the application of THz technology in the precise biomedical area. To resolve this problem, we designed and fabricated core components, and built a new super-resolution THz spectral imaging instrument, termed THz-SNOM, which has a nanometer resolution. We also achieved high-performance THz probes based on theoretical simulations and micro-nano fabrication techniques. Further, we discovered that graphene was an excellent substrate for single proteins in THz-SNOM imaging. Finally, we successfully investigated single proteins with THz-SNOM, and obtained the THz images and spectra of individual immunoglobulin G and ferritin molecules. The demonstrated strategy thus opens new routes to imaging single biomolecules with THz.

Huabin Wang
Professor
Chongqing Institute of Green and Intelligent Technology, Chinese Academy of Sciences, China

Prof. Huabin Wang is the Deputy Secretary-general of Terahertz Biophysics, Biophysical Society of China, the director of the Center of Super-Resolution Optics, CAS, and the State Council Special Allowances Expert. He presided over important and competitive projects such as the National Key Research and Development Program, and the National Natural Science Foundation. His research is focused on terahertz instrumentation and application. He has authored/co-authored ~100 scientific articles published in PNAS, ACS Nano, Biosensors and Bioelectronics, etc.

[AI-2] PIBM2024-0415-1

AttoNewton force sensing by ion-resonance optical tweezers

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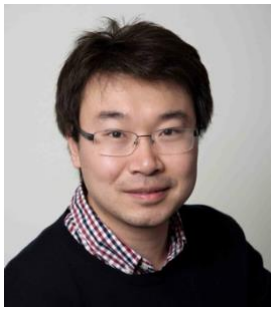
Abstract: Optical tweezers are invaluable for manipulating small particles and detecting minute forces. Modern nanomaterial advancements expand their capabilities, introducing modalities like temperature and pH sensing. Yet, the challenge persists in achieving efficient 3D manipulation of nanoparticles due to their limited polarizability at the nanoscale, resulting in low trapping efficiency. Here, we present a lanthanoid ion resonance effect on nanoparticles to address the challenge and expand the force-sensing capability. By introducing the resonance effect to enhance optical trapping forces, a maximum optical trap stiffness of 0.086 pN μm^{-1} mW^{-1} for 23.3 nm nanoparticles has been achieved. This approach surpasses reported values for gold nanoparticles. Building on this breakthrough, the study extends the application of this novel probe to enhance precise force measurement in aqueous solutions, employing fluorescence video tracking of ion-resonance nanoparticles and pushing the boundaries of nanoscale force sensing to its thermal limit. We further demonstrated that the resonance effect can engineer the scattering properties and could be used to create dual-modality interferometric scattering microscopy.



Fan Wang
Professor
Beihang University, China

Fan Wang is a professor at Beihang University, China, leading a biophotonics research group. He has been working in the field of photonics and biophotonics technologies, including optical tweezers, super-resolution microscopy, optical sensing and computational imaging. Prof. Wang has published over 95 peer-reviewed journal articles, including 10 Nature series articles. He was awarded a Chinese overseas young talent project, the Australia Discovery Early Career Researcher Award, the David Syme research prize and the iCANX Young Scientist Awards. His expertise is recognized through more than 20 invited talks at conferences and a Light People character interview by Light: Science & Applications.

[AI-3] PIBM2024-1016-1

Real-Time Monitoring of Small Extracellular Vesicles (sEVs) by *In vivo* Flow Cytometry

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Abstract: Small extracellular vesicles (sEVs) are complex biomolecular delivery systems that reflect the biological characteristics of their cells of origin and possess significant potential for clinical applications. Their ability to carry molecular signatures and circulate throughout the body makes them ideal candidates for non-invasive biomarkers in diagnosing various diseases through blood tests. In addition, sEVs can serve as drug delivery vehicles, capable of encapsulating a variety of low molecular weight drugs, exogenous RNA, small proteins, and more. However, the detection of sEVs presents technical challenges due to their nanoscale particle size limitations, especially in the context of *in vivo* monitoring. *In vivo* flow cytometry (IVFC) is a device that employs optical methods to monitor particles in the blood circulation, thereby enabling the real-time monitoring of sEVs *in vivo*. In this study, it was demonstrated that the concentration of sEVs can be analyzed by measuring the baseline height of the IVFC signal, while the agglomeration of sEVs can be assessed by counting the number of signal peaks. If sEVs are taken up by cells, peak signals will also be generated. *In vivo* monitoring of PEG-modified sEVs was conducted using IVFC. Analysis of the signal baseline indicated that modified sEVs were cleared more slowly from the bloodstream, while analysis of the signal peaks showed reduced clustering of these modified sEVs. In conclusion, IVFC can monitor sEVs in blood circulation in real time, facilitating the study of sEV drug loading and providing a crucial basis for personalized therapy and new drug development.

Xunbin Wei

Professor

Peking University, China

Dr. Wei completed his post-doc at Harvard Medical School. He was a professor in Fudan University, China. From 2011-2019, he was a professor and chair in Department of Biomedical Instrumentation, School of Biomedical Engineering, Shanghai Jiao Tong University. Currently, he is a professor at Department of Biomedical Engineering, Institute of Clinical Advanced Medicine, Peking University. Dr. Wei is an SPIE Fellow, and recipient of Chinese Outstanding Young Scholar Award. He has published more than 100 peer-reviewed papers, including in Nature and PNAS. His interests include cancer detection by optical means, optical manipulation of cells, and light treatment of Alzheimer disease.

[AI-4] PIBM2024-0819-13

Microfluidics with optical detection for highly efficient *in vitro* diagnosis

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Abstract: The emerging microfluidics has the potential to revolutionize in vitro Diagnosis (IVD) due to its high throughput, parallelism, rapidity, accuracy, and user-friendly operation. In this presentation, we introduced our recent advancements on microfluidics-based methods for IVD systems coupling with optical detection schemes. Emphasis would be placed on how to design fully integrated microchip for achieving nucleic acids analysis or molecular diagnosis, immunoassay and antibiotic susceptibility testing. Commercialization for real medical application was also included. Some special considerations for on-site analysis or point-of-care-testing were discussed. We believe that microfluidics holds great potential for wide applications in precision medicine including high-throughput biochemical analysis, molecular and immune diagnostics, and drug susceptibility testing.

[AI-5] PIBM2024-0629-1

Surface plasmon based analytical methods and medical applicaitons

Xiangwei Zhao

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Abstract: Surface plasmon (SP) derives from the interaction of light and matter at nanoscale accompanied by novel physical phenomena, which enables localized surface plasmon resonance, surface enchanced Raman spectrum and so on. In our study, we utilized this in biomedical applications like biosensing, bioimaging and biomanipulations. By engineering plasmonic materials and their nanostructure, as well as factors that affect the surface plasmon propagation, we showed that high sensitive biosensing of molecules and cells could be realized for convenient and rapid point of care testing (POCT) and single cell could be manipulated by SP as well. Also, SP could help gaining the molecule fingerprinting profiles of tissues in combination with spatial bio-omics data.

Xiangwei Zhao
Professor
Southeast University, China

Xiangwei Zhao is a professor of State Key Laboratory of Digital Medical Engineering, Southeast University. His research focus on biomedical detection and analysis, including bionanophotonics, spatial omics, etc. He has won Natural Science Prize of the Ministry of Education (First Class), Huanjiasi Biomedical Engineering Prize of Chinese Society of Biomedical Engineering (Second Class) and Gold Medal of the Geneva International Invention Exhibition.

[AI-6] PIBM2024-0728-3

Computational volumetric Raman imaging

Xueli Chen[1,2], Nan Wang[1], and Gong Feng[1]

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Abstract: Rapid quantitative volumetric imaging is important in the study of three-dimensional (3D) complex bio-systems, including cell biology, neuroscience, and tumor research. Light sheet microscopy and optical projection tomography are two typical methods to achieve rapid quantitative volumetric imaging, but both techniques require fluorescent labelling to identify 3D chemical composition of a complex bio-system. Based on the development of Raman scattering effect and projection tomography, combining projection tomography strategy with Raman spectroscopic imaging can achieve high-speed, label-free, and high-resolution volumetric chemical imaging of large-volume complex systems. Firstly, by combining the projection tomography strategy with the stimulated Raman scattering microscopy technique, the Bessel beam-based stimulated Raman projection tomography technique is developed, which can achieve high-speed, high-resolution, and label-free quantitative microscopic imaging of 3D volumetric samples. Secondly, a dual-mode optical-Raman projection tomography technique was developed by combining the projection tomography strategy with wide-field Raman spectroscopic imaging, which can achieve high-speed, high-resolution, label-free quantitative microimaging of 3D volumetric samples. Finally, considering the sample fixation complexity of the projection tomography technique, a volumetric Raman imaging technique based on light-field architecture was developed, which, combined with the assistance of artificial intelligence algorithms, can realize 3D imaging with micrometer-level spatial resolution without complex sample fixation.

[AI-7] PIBM2024-0820-21

Low-power, single-CW-beam, three-dimensional Super-resolution Fluorescence Microscopy

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Abstract: The optical microscopy resolution is limited by the physics of diffraction, $d=\lambda/2n\sin\theta$. The N-photon microscopy can theoretically improve resolution, $d=\lambda/(2n\sin\theta N^{1/2})$. However, this is a paradox that higher N always means longer λ_{ex}. To break this limit, we proposed 730-nm CW laser excited 4-photon microscopy, obtaining 161-nm sub-diffraction resolution. Photon avalanche (PA) occurring in lanthanide-doped solids is a very important mechanism, which can arouse a giant nonlinear response. The achievement of PA, mostly restricted to bulk materials, conventionally relies on very sophisticated excitation schemes, individual for each PA system. Recently, we established a universal PA strategy to generate huge optical nonlinearities from various emitters, i.e., migrating photon avalanche (MPA). PA are synchronously achieved for both Yb^{3+} and Pr^{3+} ions, exhibiting a 26^{th} order nonlinearity and a clear pumping threshold. The avalanching Yb^{3+} ions can migrate their optical nonlinear response in a long range to other emitters located in the subsequent shell layer, resulting in a higher order nonlinearity of up to 63^{rd}. Further cascading a Gd^{3+} sublattice migrating network (cMPA), its avalanching energy can propagate among various emitters in multilayered nanostructures, leading to full-spectrum extremely-nonlinear emissions. As a demonstration, using one low-power, 852-nm CW beam, we implemented dual-color sub-diffraction super-resolution nanoscopic imaging with a lateral resolution down to 58 nm and an axial resolution down to 185 nm. Resolution anisotropy stems fundamentally from the limited aperture angle of the objective lens. To achieve isotropic super resolution imaging, we present a conceptually novel strategy of mirror-assisted self-interference field excitation (SIEx) highly-nonlinear microscopy, achieving a lateral resolution down to 54 nm (λ/15) and an axial resolution down to 57 nm (λ/15) with one single low-power CW beam (19 $kW\cdot cm^{-2}$). Our developed low-power, single-CW-beam, 3D nanoscopy can be in principle integrated with the existing and widely available laser-scanning fluorescence microscope without adding any complexity, thereby enabling their capability of isotopic super-resolution 3D imaging.

Qiuqiang Zhan
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Qiuqiang Zhan is currently a professor of optics in South China Normal University, China. He received a B.S. in Optics from Shandong University, and performed his doctoral research in the Optical Engineering department at Zhejiang University. He had visiting research in Lund University, Sweden and the Chinese University of Hong Kong. He has long been devoted to the research of super-resolution, large-depth and high-speed fluorescence bioimaging based on near-infrared photon upconversion, and has achieved a series of original academic achievements. As the first/corresponding author, he has published 50 peer-reviewed journal (including *Nat. Nanotechnology, Nat. Communications*) papers, some of which are ESI highly-cited papers. He has been authorized 18 Chinese invention patents and won some awards for his creative work, including “National Excellent Young Scholars” “Distinguished Young Scholars of Guangdong”, “Hong Kong Scholar award” and “Youth Innovation Award”.

Immunophotonics

[II-2] PIBM2024-0730-15

Engineering of radiation-derivatives for anti-tumor immunotherapy

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Abstract: This study focuses on addressing the issue of low indications for radiotherapy in the treatment of widely metastatic late stage tumors, with a specific focus on the analysis of classic phenomena in radiotherapy, the exploration of direct and indirect (vaccine effect) anti-tumor effects of radiotherapy products, and the conduct of basic and translational interdisciplinary research on radiotherapy-derived materials. Using several imaging models and strategies, the following results were obtained. 1) The new mechanisms underlying bystander and abscopal effects of radiotherapy were elucidated, and an original concept of indirect radiotherapy based on radiotherapy products was proposed; 2) Several novel targets for immune cell regulation and radiation-derived substances with immunomodulatory capabilities were discovered, leading to the development of a series of radiotherapy-derived nanomaterials for immunotherapy of advanced tumors; 3) Irradiated cell membranes, radiated tumor cell‐released microparticles, radiotherapy ultrasound fragments were found to be efficient antigens for vaccines, upon which a personalized tumor vaccine based on radiotherapy was constructed. This research provides a new avenue of indirect radiotherapy for advanced tumor patients who cannot undergo clinical radiotherapy.

Honglin Jin is a professor in the School of Biomedical and Health at Huazhong Agricultural University (HZAU). He graduated from the Wuhan National Laboratory for Optoelectronics, Huazhong University of science and technology (HUST). During the year 2014 to 2021 (before April), he has worked in the cancer center of Wuhan Union Hospital, affiliated with HUST. In April 2021, he was transferred to HZAU. He has received the support of the excellent youth fund of the National Natural Science Foundation of China. His lab focuses on developing bioinspired and biomimetic materials for cancer immunotherapy. As the first or corresponding author, he has published over 50 SCI-indexed papers, including Science Advances, Advanced Materials, Nano Today, Advanced Science, EMBO Molecular Medicine, ACS nano, Angew Chem, JCI insight and Int J Radiat Oncol.

[II-3] PIBM2024-0810-1

Biomimetic Porphyrin Nanoparticles

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Abstract: The biomimetic nanoparticle represents a pioneering drug delivery platform inspired by natural biological features, aiming to enhance both the biocompatibility and specificity of nanotechnology in delivering drugs to targeted diseases. Here, we present multiple porphyrin biomimetic systems designed to mimic natural biological attributes for theranostic applications.

The porphyrin-based ultra-small nanostructure, known as PLP, mimics natural lipoproteins and inherently combines positron emission tomography, fluorescence, and photodynamic therapy functions for theranostic purposes [1-2]. PLP's biomimetic nature exhibits favorable pharmacokinetics without requiring PEGylation. Its rapid tumor intracellular trafficking enables nanostructure dissociation upon tumor accumulation, releasing monomeric porphyrins for low-background near-infrared fluorescence imaging and activatable photodynamic therapy.

To address the challenges in glioblastoma treatment, such as penetrating the blood-brain barrier (BBB) and achieving precise tumor targeting, we utilized the properties of endogenous apolipoprotein E3 (apoE3). Acting as a natural apolipoprotein, apoE3 facilitated the transcytosis of nanoparticles across the BBB and established strong interactions with glioblastoma cells that overexpress the low-density lipoprotein receptor. This strategic approach resulted in the development of glioblastoma-targeted porphyrin-lipid apoE3 lipid nanoparticles with inherent theranostic properties [3].

Furthermore, we engineered a nanoagent with a dual-biomimetic system: (1) mimicking efficient light-harvesting organelles found in nature, chlorosomes, with unique dye supramolecular assemblies and tunable photonic properties, and (2) mimicking high-density lipoproteins to stabilize intact dye assemblies and impart favorable in vivo behavior [4]. This dual-biomimetic system enables precise control over particle size and optical properties, facilitating tunable mouse bioimaging (photoacoustic/fluorescence imaging) and phototherapies (photothermal /photodynamic therapies).

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Dr. Juan Chen received her B.Sc. in Polymer Chemistry from Shandong University, China, and her Ph.D. in Applied Chemistry from the Research Institute of Petrochemical Processing. Following that, she joined Dr. Gang Zheng's laboratory at the University of Pennsylvania in 2003; there she undertook a three-year postdoctoral fellowship program in the Department of Radiology. During this period, Dr. Chen began her research program in the field of molecular imaging and has made significant contributions on the development of photodynamic molecular beacons and biomimetic lipoprotein-like nanoparticles. Since 2006, Dr. Chen has been a Scientific Associate at the University Health Network, she is currently the research project manager of Dr. Zheng's lab, and runs the NanoMedFab facility. She possesses great expertise in porphyrin chemistry, lipid-nanoparticle engineering, and the design of smart probes for targeted and activatable molecular imaging and phototherapy of cancer. Dr. Chen has published over 100 high-impact research articles in the field of nanomedicine.

[II-4] PIBM2024-0725-1

Fluorescent/circular dichroic dual-mode chiral upconversion nanocomposite for the diagnosis and treatment of rheumatoid arthritis

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Abstract: Chiral nanophotonic materials are ideal candidates for biosensing applications, and their use in disease diagnosis and treatment has garnered widespread attention. Herein, we present an upconversion nanoparticles (UCNPs)-based chiral nanocomposite (UCNPs@L-POM) with both upconversion luminescence (UCL) and circular dichroism (CD) signals. By using L-Cysteine (L-Cys) as both reducing agent and chiral ligand, the oxidative molybdenum-based polyoxometalates (Ox-POM) automatically coat on the surface of UCNPs to form chiral nanocomposite. In the presence of hydroxyl radical (·OH), the Mo element in the nanocomposite is oxidized, leading to the quenching of UCL. Simultaneously, the dissociation of L-Cys results in the change of CD signal, enabling dual-mode sensing of UCL/CD signals on ·OH. The detection limits of the two modes in aqueous solution are 6.352 μM and 0.912 μM, respectively. This dual-mode sensing capability can also be applied at the cellular level. As a demonstration, UCNPs@L-POM can achieve in suit imaging diagnosis of rheumatoid arthritis (RA) with high ·OH expression. Additionally, based on the oxidation reaction caused by ·OH, UCNPs@L-POM can effectively alleviate paw inflammation and promote the healing of RA. This study provides a new prospect for biological applications of chiral nanocomposites.

Xiaomin Liu
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Xiaomin Liu is "Tang Aoqing Scholar" distinguished Professor of Jilin University. She focused on the basic scientific problems in the research field of rare earth upconversion nanoluminescence and practical problems in application, she carried out in-depth and systematic research in the fields of synthesis methods, composite structure design, upconversion energy migration mechanism and dynamics, innovative loading methods of nanocarriers, new biomedical detection technologies of upconversion fluorescence resonance energy transfer, and new bioimage-guided photodynamic treatment of tumors, and has profound accumulation and rich experience. Xiaomin Liu has published 75 SCI indexed papers in important international academic journals, including *Chem. Soc. Rev.*, *ACS Nano*, *Angew. Chem. Int. Ed.*. She has applied for and authorized 25 invention patents. Besides, she was recommended as an international member of the EU Science and Technology Cooperation Program (COST). She won the funding of the Sino-Dutch Intergovernmental Joint Research Plan, National Natural Science Foundation Joint Fund, general project, youth project, and the Leading Talents and innovation team project of Jilin.

Neurophotonics

[NI-1] PIBM2024-0730-1

High throughput 3D imaging of miniatured model animals by a light-sheet fluidic imaging system

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Abstract: As a widely used miniatured model animal in the study of the development, disease mechanisms, and drug screening, zebrafish possess characteristics of a short reproductive cycle and large-scale culturing capability. However, there is currently a lack of high-throughput 3D imaging instruments, posing a bottleneck for large-scale characterization and analysis. To address this, we developed a high-throughput 3D imaging system based on fluidic flow and light-sheet illumination. This system can achieve high-throughput, fully automated 3D imaging at cellular resolution of hundreds of zebrafish embryo samples within half an hour. We also developed 3D registration and segmentation algorithms for the vast amount 3D image data. An enhanced deep learning U-Net network segment and quantitatively analyze the structure of trunk and brain vasculature. Using the imaging system and algorithms, we studied the heterogeneity in zebrafish vascular development and the effects of angiogenesis inhibitors. The results demonstrated the necessity of high-throughput characterization in developmental mechanisms and drug screening, as well as the powerful capabilities of this high-throughput 3D imaging system.

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Prof. Hui Li received his Ph.D. degree from the Institute of Physics, Chinese Academy of Science, then worked as a research associate at the University of Konstanz (Germany), Iowa State University, and the University of Notre Dame. In 2013, he joined Suzhou Institute of Biomedical Engineering and Technology (SIBET), Chinese Academy of Sciences. In 2023, He joined Ningbo Institute of Materials Technology and Engineering, CAS. His research mainly focused on optical imaging techniques and instrumentation, including structured illumination super-resolution microscopy, high throughput light-sheet flow imaging system, meta-lens for miniature microscopy, as well as computational microscopy.

[NI-2] PIBM2024-0820-16

Specific control of calcium channels solely by femtosecond laser in vitro and in vivo

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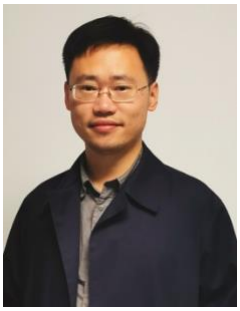
Abstract: Ca^{2+} channels can be externally activated by optogenetics, but it requires robust introduction of exogenous optogenetic genes. Here we present femtoSOC, a method for direct control of Ca2+ channels solely by ultrafast laser without the need for optogenetic tools or any other exogenous reagents. Specifically, by focusing and scanning wavelength-tuned low-power femtosecond laser pulses on the plasma membrane for multiphoton excitation, we directly induced photoexcited flavin bonding with cysteine in Orai1 that then polymerize to form store-operated calcium channels (SOCs). By this method, we achieve to activate an individual neuron in a cortical ensemble in layer 2/3 of the primary visual cortex (V1), which, in the absence of any visual stimuli, is sufficient to elicit visually percept-specific behaviors in awake mice, without co-activating other neurons in the ensemble in layer 2/3 of V1. Remarkably, the disruption of a single neuron within the ensemble temporarily paralyzes the entire ensemble and suspends behavioral responses to visual stimuli. However, the ensemble rapidly recovers its responsiveness and effectively maintains the internal representations necessary for these behaviors. Consequently, individual neurons in ensembles appear to function as fully functional units, redundantly supporting both the internal representations and the robustness of the entire ensemble. Furthermore, we reveal the existence of a Ca^{2+} channel in nuclear envelope (NE) by developing an optical technique, termed Ca^{2+} release in microdomain evoked by laser (CaMEL) that activates a local Ca^{2+} rise restricted to a cytosolic microdomain while maintaining intracellular Ca2+ homeostasis.



Hao He

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Prof. Hao He is the full-time professor in the school of Biomedical Engineering, Shanghai Jiao Tong University. He got the B.S. from the University of Science & Technology of China and Ph.D from the Chinese University of Hong Kong. His research interest focuses in the optical control technology of calcium channels and the biological applications. He has published more than 50 peer-reviewed journal papers.

[NI-3] PIBM2024-0507-1

Dual-Color Pulsed Laser Excitation for the Photobiomodulation of Traumatic Brain Injury

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Abstract: Photobiomodulation (PBM), also known as low-level laser therapy (LLLT), represents a promising non-invasive physical therapeutic strategy for the intervention of various neurological and psychiatric disorders, such as traumatic brain injury (TBI), AD and depression. Differential therapeutic outcomes arise when triggered by pulsed lasers with various wavelengths.

In this study, the specific impact of combined 808nm and 1064nm lasers with pulsed excitation on TBI was inspected. It is expected that PBM by using combined 808nm and 1064nm pulsed laser excitation might ameliorate core TBI symptoms. Firstly, laser irritation parameters used were optimized by examining the wound healing and vascular angiogenesis. And then we discovered that that TBI mice group under the intervention by combined two-color laser exhibited improved cognitive and motor function according to the rotarod test, reduced anxiety levels in the open-field test, and enhanced cognitive function assessed via the Barnes test indicated as compared to other treatment groups. Notably, combined laser therapy demonstrated the capability to protect the blood-brain barrier and boost ATP levels, facilitating the recovery of traumatized regions. Further, two-color PBM is able to promote microglial activation and reduce neuroinflammation. Importantly, the therapeutic efficacy of PBM to TBI, is significantly enhanced when using dual-wavelength 808nm and 1064nm laser irritation, offering novel insights into the biological mechanisms for potential clinical translations.

Zhen Yuan

Professor

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Dr. Yuan is a full professor with the Faculty of Health Sciences (FHS)/Centre for Cognitive and Brain Sciences at University of Macau (UM). His research mainly focuses on biomedical optics, optical molecular imaging, neurophotonics and neuroimaging. Professor Yuan has published over 300 papers in high profile journals in his field such as Science Advances, Nature Communication, Research, Microbiome, Journal of Behavioral Addictions, Psychological Medicine, Neuroimage, Cerebral Cortex, Cortex, Human Brain Mapping, Small, Advanced Functional Materials, Nano Letters, ACS Nano, Biomaterials, Angewandte Chemie International Edition, Theranostics, Optics Letters, Optics Express, and Applied Physics Letters. His google H-index is 56 and total citation is 10000. He is the editorial board member of Quantitative Imaging in Medicine and Surgery, associate editor of BMC Medical Imaging, and associate editor of Frontiers in Human Neuroscience. He is a senior member of OSA and senior member of SPIE.

[NI-4] PIBM2024-0729-12

Optical manipulations for precision cell/neural stimulation and regulation

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Abstract: Neural stimulation and modulation at high spatial resolution are crucial for mediating neuronal signaling and plasticity, aiding in a better understanding of neuronal dysfunction and neurodegenerative diseases. In this talk, I will share our recent progresses on precision cell/neural stimulation and regulation. We developed new methods based on optical manipulations for precision cell/neural stimulation and regulation. Our techniques enables the precision neural stimulation and regulation with single-cell or subcellular precision.

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Dr. Hongbao Xin is currently a professor, Vice-Dean of the College of Physics & Optoelectronic Engineering and Vice Director of the Institute of Nanophotonics, Jinan University, Guangzhou, China. He is a Young Changjiang Scholar. He received his BS degree and Ph.D degree at Sun Yat-sen University. After graduation, he continued his research at the University of California, Berkeley and the National University of Singapore. He joined Jinan University in 2018. His research interests focus on biophotonics and nanophotonics, such as optical tweezers for bio-optical manipulation and regulation, plasmonic nanoantenna for bio-detection. He has published about 60 peer-reviewed journal articles, including Nature Photonics, Nature Reviews Materials, Nature Communications, Advanced Materials, Light: Science & Applications, Nano Letters, etc. He serves as the Associate Editor of Optics Express.

[NI-5] PIBM2024-0805-1

Towards Bidirectional Optical Brain Interfaces

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Abstract: Bidirectional optical brain interfaces, the integration of neural imaging and optogenetics stimulation, is promising to resolve functional connection of neural circuits in vivo. However, due to physical limitations of the imaging hardware and tissue optics, current optical methods meet bottlenecks in speed, depth, and scale, etc. In this talk, I will introduce our recent efforts toward this exciting field, including random-access wide-field microscopy, scanning wide-field tomography, cross-region all-optical physiology, and brain-to-brain interfaces, etc.

[NI-6]

Transcranial photobiomodulation improved brain function in healthy older adults

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Abstract: Transcranial photobiomodulation (tPBM) is a noninvasive method using low-power lasers or LEDs to target the brain. Our study involved 105 healthy older adults (49–79 years) using functional near-infrared spectroscopy (fNIRS) to examine tPBM effects on brain function during resting state and a digit n-back working memory (WM) task. Results showed that both single and seven-day repeated tPBM improved WM performance. Single tPBM enhanced resting-state connectivity and seven-day tPBM improved global network efficiency. Additionally, a single session reduced brain activation in contralateral areas and repeated sessions extended this reduction. Moreover, both single and repeated tPBM decreased brain signal variability. Finally, these changes in brain function correlated with WM improvements.

[NI-7] PIBM2024-0730-25

Pushing Microscopy Boundaries of Superconducting Nanowire Single Photon Detectors for Deep In Vivo Near-Infrared Imaging

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Abstract: We review Single Quantum's recent efforts to apply superconducting nanowire single-photon detectors (SNSPDs) to the field of (bio)imaging.

We review the efforts of Single Quantum and their collaborators to employ SNSPDs for effective confocal fluorescence imaging of live mice in the short-wave infrared (SWIR) range, where scattering and absorption of biological tissue are reduced compared with the visible range. In this wavelength range, SNSPDs dramatically outperform competing photon detection technologies, providing a combination of high quantum efficiency (>70%), low dark-count rates (<100 cps) and tens of picosecond time resolution. We show that the mature technology of SNSPDs allows for one-photon confocal fluorescence imaging of deep structures in the mouse brain, achieving a signal to background ratio of 1 at 1.3 mm depth. Furthermore, by shifting the fluorescence excitation and emission wavelengths to the 1.6 µm-1.9 µm range we achieve 1.1 mm-depth imaging in an ***intact*** mouse brain, i.e. non-invasive deep imaging.

Building on successful one-photon imaging at greater depths, through the EU-funded project Brainiaqs, we developed an innovative free-space-coupled array of SNSPDs that what used to build a two-photon microscope that operates completely in the SWIR wavelength range: **both** excitation and emission wavelengths for two-photon excitation are in the SWIR range. With such a microscope we image the brain of a live mouse at depths of 0.9 mm, comparable with commercially available two-photon microscopes. We also present results obtained with a 1D SNSPD array that allows for the simultaneous acquisition of spectra, lifetimes, photon correlations and cross correlations in one measurement with unprecedented performances in the SWIR.

In summary, our results underscore the transformative potential of various devices based on SNSPDs for in vivo bioimaging within the SWIR spectrum.

Val Zwiller

Professor

KTH Royal Institute of Technology, Sweden

Val got his PhD from Lund University, Sweden in 2001 on the generation of single photons with quantum dot devices. He was a postdoc at the Humboldt University in Berlin Germany, an assistant at EPFL, ober-assistant at ETH Zurich in Switzerland before starting his group at TU Delft in the Netherlands in 2005 on single photon technology. Val moved to KTH Stockholm, Sweden in 2015 to lead the Quantum Nano Photonics group as a full professor. Val co-founded Single Quantum BV in 2012 to develop high-performance single photon detectors and Quantum Scopes AB in 2021 to develop quantum instruments.

[NI-8] PIBM2024-0925-1

Single-neuron and whole-brain mapping of the arcuate fasciculus in macaque monkeys: insights into human homologous organization

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Abstract: The pathways and connectivity profiles of the arcuate fasciculus (AF) in nonhuman primates remain debated, particularly regarding its divergence from the human homolog. Here we employed a viral-based genetic labeling strategy in macaque brains alongside fluorescence micro-optical sectioning tomography to develop a cross-scale method for single-neuron tracing of AF, and compared with brain-wide tractography from 11.7T diffusion MRI. Additionally, a spectral embedding analysis using 7.0T diffusion MRI data from humans enabled an interspecies comparison of AF connectomes. Our findings reveal that the macaque AF originates in the temporal-parietal area, passes through the auditory cortex and around parietal operculum, and extends into prefrontal regions. Notably, the human AF exhibits a more extensive expansion into the middle temporal gyrus, with increased connectivity that contributes to species-specific differences in the prefrontal cortex and parietal operculum. These differences underscore the critical role of AF expansion and differentiation in the evolution of human language capabilities.

Translational Biophotonics

[TI-1] PIBM2024-0730-22

Real-time Photoacoustic 3D imaging

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Abstract: In this study, we report a Photoacoustic real-time 3D imaging system. This system can provide real-time imaging of entire organs of a live animal without motion artifacts. Both functional and anatomical imaging can be successfully acquired simultaneously. The spatial resolution is better than 200 μm and the field of view is no less than 2cm, making it full-body imaging capability for small animal study. We implemented this powerful imaging platform to study multiple biomedical projects, including molecular agents delivery in organs, heart beating, and brain neuroactivities. Our results demonstrate this system is a powerful biomedical imaging platform for various studies.

[TI-2] PIBM2024-0731-2

Deep-tissue optical imaging and stimulation with wavefront shaping-empowered multimode fiber

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Abstract: The usage of light has considerably reshaped the landscape of biomedicine due to its extreme sensitivity to tissue changes. Its applications in deep tissue, however, is handicapped by strong optical scattering of light in biological tissue, which results in inherent tradeoff between penetration depth and spatial resolution. Existing schemes like GRIN lens-based micro endoscopes have been developed to yield more confined delivery of light into deep tissue, but tissue damage caused by the insertion of the bulky components cannot be ignored. In this talk, we present our recent efforts in focusing and manipulation of diffused light into deep tissue through an ultrathin multimode fiber, which is empowered by optical wavefront shaping to achieve light focusing and rapid raster scanning without mechanical movement at the distal end of the multimode fiber. Whilst still in infancy, we believe that with future technological and hardware updates, along with continuous efforts, we will get closer to mature and useful application goals. This may also inspire new application ideas, bringing new concepts and opportunities that open up new venues for noninvasive or minimally invasive optical imaging and treatment of used-to-be optically inaccessible deep tissue regimes.

Puxiang Lai

Professor

Hong Kong Polytechnic University, Hong Kong SAR, China

Professor Puxiang Lai, currently at the Department of Biomedical Engineering at the Hong Kong Polytechnic University, has research interests focusing on deep-tissue optical focusing, imaging, stimulation, and treatment. His ongoing research projects include, but are not limited to, wavefront shaping, photoacoustic imaging, neuron stimulation, computational optics, and artificial intelligence. His research has fueled more than 100 top journal publications, such as Nature Photonics, Nature Communications, Light: Science & Applications, PhotoniX, Advanced Photonics, Advanced Science, and The Innovation. He has been invited to give more than 100 seminars or invited talks worldwide. Dr. Lai was awarded the 2016 National (Youth) Talent Award and the 2016-2017 Hong Kong RGC Early Career Award. As a recognition for his contribution to the field, currently Puxiang serves as Associate Editor or Editor for a few premium journals, such as The Innovation, The Innovation Medicine, Advanced Photonics Nexus, Advanced Imaging, Journal of Visual Computing for Industry, Biomedicine, and Art (VCIBA), and Journal of Innovative Optics in Health and Science (JIOHS). He is also a Guest Professor of Southern Medical University (China).

[TI-3] PIBM2024-0723-1

The application of photoacoustic computed tomography in breast surgery and vascular surgery

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Abstract: Photoacoustic computed tomography (PACT) can be used in conjunction with ultrasound (US) imaging to provide multicolor contrasts from intrinsic tissues and externally administered contrast agents. We have developed PACT systems optimized for clinical use, featuring improved sensitivity and image quality. In this study, we demonstrated enhanced visibility and detectability of breast sentinel lymph nodes labeled with carbon nanoparticles and breast tumors labeled with metal marker clips using a PACT/US dual-modality imaging system. Additionally, we applied a PACT system specifically designed for human foot imaging to visualize the foot vascular structures in patients with diabetic foot. This new technology proved effective in providing more accurate and quantitative diagnoses of the disease and evaluating surgical outcomes.

Cheng Ma
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Cheng Ma received his B.S. in Electronic Engineering from Tsinghua University in 2004 and his Ph.D. from Virginia Tech in 2012. He completed postdoctoral research at Washington University in St. Louis from 2012 to 2016. Since 2016, he has been with the Department of Electronic Engineering at Tsinghua University, where he became a tenured associate professor in 2023. His research focuses on biomedical optical imaging and its clinical applications, particularly in photoacoustic imaging and wavefront shaping.

[TI-4] PIBM2024-0724-2

Advancing photoacoustic microscopy: Technology development, artificial intelligence, and innovative applications

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Abstract: Photoacoustic microscopy (PAM) is an emerging imaging modality that offers high contrast, high spatial resolution, and three-dimensional imaging. PAM is highly effective for acquiring molecular information through either endogenous absorption, such as hemoglobin, or exogenous absorption, including contrast agents or probes, which can extract important physiological and pathological information. Our lab has been devoted to advancing PAM technology, including hardware development and artificial intelligence integration, and exploring its applications in recent years. In this presentation, I will introduce representative work and progress in these areas. For technology development, we have focused on several aspects, from devices to imaging systems. Notably, we developed fast and sensitive PAM systems using MEMS scanning and optimized the design of the imaging head. Additionally, we devised a miniature non-contact PAM imaging probe based on photoacoustic remote sensing for imaging cerebral blood vessels. To enhance PAM with artificial intelligence, we developed deep learning models for processing sparse and noisy PAM images. For PAM applications, we have explored several intriguing applications of PAM. For instance, we studied germanium nanoparticles as contrast agents of PAM and demonstrated their use in tumor imaging and photothermal therapy. PAM was also employed to investigate disease models, such as blood disorders in zebrafish and placenta disease models in mice. Furthermore, we explored PAM for industrial non-destructive testing, specifically for in-situ and in-operando imaging of lithium metal batteries, highlighting PAM's potential of PAM to study battery cycling and failure mechanisms. In summary, our work demonstrates the advancements in PAM technology and its diverse and promising applications in both biomedical and industrial fields.

Sung-Liang Chen
Associate Professor
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Sung-Liang Chen is an Associate Professor at the University of Michigan-Shanghai Jiao Tong University Joint Institute, Shanghai Jiao Tong University. He received his Ph.D. degree in electrical engineering from the University of Michigan, followed by post-doctoral training at the University of Michigan Medical School. In 2013, he joined Shanghai Jiao Tong University as a principal investigator. His research interests include optical neural networks, artificial intelligence for optical microscopy and medical imaging, and photoacoustic imaging technology and applications. Dr. Chen has published more than 60 peer-reviewed articles in journals such as Nature Photonics, IEEE TMI, Analytical Chemistry, Photoacoustics, and Nanoscale. He holds 3 granted Chinese invention patents. He was awarded the Shanghai Pujiang Talent Award in 2014 and the National Talents Program for young professionals in 2015.

[TI-5] PIBM2024-0812-1

Multimodal Photoacoustic Tomography of Breast Tumor for Improved Early Diagnosis

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Abstract: Recognizing the pivotal role of early and precise breast tumor diagnosis is essential, yet current imaging techniques, such as mammography, ultrasonography, and magnetic resonance imaging, have inherent limitations. These modalities often suffer from low specificity, slow imaging speeds, the application of ionizing radiation, and dependence on exogenous contrast agents, which collectively contribute to a high rate of benign biopsies—over 75% of cases.

To overcome these challenges, we have engineered a high-speed dual-modal imaging system (HDMI) aimed at significantly improving early breast tumor detection. HDMI employs a novel combination of dark-field illumination with a large-view ultrasonic array, enabling the simultaneous acquisition of panoramic photoacoustic and ultrasonic computed tomography images. This dual-contrast imaging system can complete a full breast scan in just 12 seconds, with a penetration depth exceeding 5 cm *in vivo* and impressive spatial and temporal resolutions (190 μm in-plane resolution and a 10-Hz dual-modal frame rate). HDMI's design supports standardized breast positioning, ensuring consistent imaging performance across various breast sizes, from A to F cups.

In a clinical evaluation of 155 patients with breast tumors classified as BI-RADS 3, 4, or 5 based on prior ultrasound, HDMI demonstrated substantial diagnostic improvements. By integrating photoacoustic and ultrasound image features into a diagnostic model powered by machine learning, we achieved a notable enhancement in specificity. Specifically, HDMI improved diagnostic specificity to 70.0% (99% [CI] = 48.6%–86.6%), compared to 22.5% with conventional ultrasound, representing a 47.5% increase. Moreover, HDMI's capability extends beyond tumor diagnosis. It also revealed increased angiogenesis in the contralateral breasts of breast cancer patients—a physiological marker not visible with existing imaging techniques. This finding highlights HDMI's potential to provide more comprehensive insights into breast pathology.

In summary, HDMI represents a transformative advancement in breast tumor diagnostics, delivering accurate early detection without the drawbacks associated with ionizing radiation, contrast agents, operator variability, or invasive procedures. This innovation promises to reduce unnecessary biopsies and enhance patient care.

Li Lin
Professor
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Li Lin earned his PhD degree from Caltech in 2019 under the guidance of Professor Lihong V. Wang and subsequently pursued postdoctoral research within the same laboratory. Since 2022, he has been actively engaged in his role as a principal investigator at Zhejiang University. His contributions have not only expanded the applications of photoacoustic imaging across multiple research scenarios but have also played a crucial role in enhancing the technical performance for clinical translation. Over the past few years, Li has published 8 high-impact research articles featured in renowned journals including Nature Reviews Clinical Oncology, Nature BME, Nature Communications, Light: Science & Applications, and Advanced Science.

[TI-7] PIBM2024-0813-1

High-Performance Biomedical Photoacoustic Tomography

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Abstract: Based on the energy conversion of light into sound, photoacoustic imaging is an emerging noninvasive biomedical imaging technique and has experienced explosive developments in the past two decades. As a hybrid imaging technique, photoacoustic imaging possesses distinguished optical absorption contrast as in optical imaging and superb spatial resolution as in ultrasound imaging. It can visualize biological samples at scales from organelles, cells, tissues, organs to small-animal whole body and has found unique applications in a range of biomedical fields. In this presentation, I will present our most recent progress in photoacoustic imaging, including photoacoustic tomography and photoacoustic microscopy. The work advances both the technology and applications of photoacoustic imaging in biomedicine.

[TI-6] PIBM2024-0731-17

Real-time 3D deconvolutional photoacoustic image reconstruction based on Kirchhoff diffraction extrapolation

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Abstract: Photoacoustic computed tomography (PACT) provides non-invasive, high-specificity, and high-resolution imaging of internal human microstructures, showing considerable promise for clinical applications. Nevertheless, the speed of 3D photoacoustic image reconstruction is hindered by substantial computational demands, while imaging quality is affected by the limited view of detection and effective field of view. This paper introduces a Kirchhoff diffraction extrapolation-based deconvolution (KDED) algorithm for photoacoustic image reconstruction. Our approach addresses the limitations of traditional back-projection and deconvolution algorithms, enhancing the field-of-view, speed, and robustness to enable real-time reconstruction of full-field images with limited-view detection. Utilizing photoacoustic data from over 4000 individual detectors and Graphics Processing Units (GPUs) for parallel computing, we achieved reconstruction of a 400x400x400 3D volume in 0.5 seconds, advancing the capabilities of 3D photoacoustic imaging and setting a benchmark for real-time performance.

[TI-8] PIBM2024-1014-3

DMD High-Speed High-Precision Optical Field Modulation Technology

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Abstract: Modulating the complex amplitude of optical fields enables advanced applications like deep imaging in scattering biological tissues and holographic imaging. Rapid and high-precision control of complex amplitude optical fields represents a current challenge. In this research direction, we have extensively studied how to utilize digital light processing technology for rapid and high-precision control of complex amplitude optical field information, achieving several research outcomes, including anti-strong scattering light focusing technology based on complex wavefront modulation and control, multifocal holographic imaging technology, and multi-wavelength dispersion compensation technology. Additionally, we developed several digital micromirror devices, providing powerful tools for optical field modulation. These studies not only deepen the understanding of the perception and manipulation of complex amplitude optical field, but also hold promise for advancing technologies in biomedical photonics, semiconductor inspection, and optical neural networks.

Dr. Jiamiao Yang, Associate Professor and Doctoral Supervisor at Shanghai Jiao Tong University, currently serves as the Director of the Intelligent Photoelectronic Sensing Institute at Shanghai Jiao Tong University. He has been selected for the "High-level Overseas Talent Introduction Plan" by the Organization Department of the Central Committee, the "Shanghai Overseas High-level Talent Introduction Plan," and the "Shanghai Pujiang Talent," and awarded the "National Outstanding Doctoral Dissertation Award" by the Chinese Instrument and Control Society. He is long engaged in research in optical detection/imaging, optical field modulation, optical computing, biomedical photonics, etc. He is the principal investigator for 16 projects including the National Natural Science Foundation of China, the Science and Technology Commission of Shanghai Municipality, Huawei Technologies Co., Ltd., and American Food Safety Detection Instrument Companies. He has published nearly 30 papers as the first author or corresponding author in prestigious international journals such as Nature Communications, Science Advances, Light: Science & Applications, Optica, and holds over 20 national invention patents.

[TI-9] PIBM2024-0730-16

Surface-Enhanced Raman Spectroscopy: A Potential Tool for Metabolomics Research

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Abstract: Surface-Enhanced Raman Spectroscopy (SERS) is advancing metabolomics with its high sensitivity and specificity, providing a non-invasive and rapid alternative to traditional metabolite analysis methods. This talk explores SERS's utility in metabolite phenotyping and quantification, showcasing its capabilities in detecting cancer biomarkers and offering insights into disease metabolism. The introduction of the "SERSome" technique[1] and digital colloid-enhanced Raman spectroscopy (dCERS)[2] addresses the challenge of signal heterogeneity, enhancing SERS's reproducibility and accuracy. SERS's potential extends to single-cell analysis, multi-omics integration, and therapeutic drug monitoring, positioning it as a promising tool in metabolomics research and clinical diagnostics.

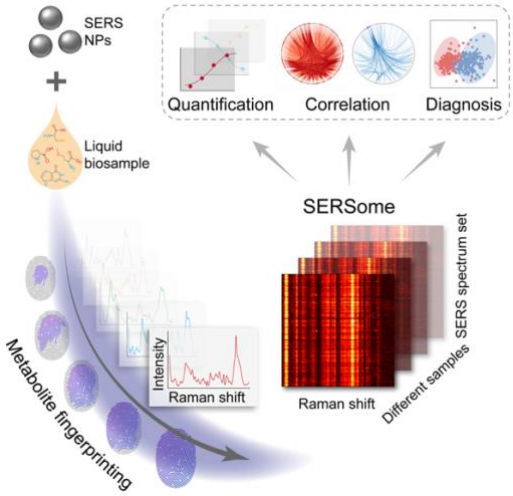

Figure 1. The concept and the workflow scheme of SERSome technique.

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[TI-10] PIBM2024-0809-3

Self-calibrated single-wavelength biosensor for measuring blood pressure

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Abstract: Nanophotonic techniques for diagnosis of a physiological tissue state are useful due to their noninvasive nature. Yet, light reflectance from a tissue is determined by the medium optical properties, absorption and scattering. Therefore, evaluating physiological parameters that correlate with absorption exclusively, requires calibration of the scattering.

Several optic methods for cuffless blood pressure (BP) measurements rely on Pulse Wave Velocity (PWV). These methods use two devices, like photoplethysmogram (PPG) and electrocardiogram (ECG) to measure the pulse wave travel time between two points in the arterial tree. These methods are based on the fact that transit time generally decreases as BP increases, but they do not directly measure BP, leading to imprecise results.

We have discovered the iso-path length (IPL) point, a specific position around a cylindrical media where the light intensity is not affected by the scattering. It was found by measuring the full scattering profile (FSP), the angular distribution of light intensity of cylindrical tissues. Therefore, when measuring in this IPL point, the absorption can be isolated from the scattering.

Based on the IPL point's principles, we designed and built an optical biosensor, constructed with a single light source and several photodetectors, as one of them is in the IPL point's location. In order to measure BP, we conducted experiments on several subjects with the biosensor placed on their upper arm, in comparison to a blood pressure monitor. The light intensity measured by the biosensor is translated into absorption coefficients, then PPG, an optic signal representing the change in blood volume in time, can be extracted, from which BP values can be calculated.

Dror Fixler

Professor

Bar Ilan University, Israel

In the biomedical field, the reemitted light intensity measured from the tissue depends on both scattering and absorption. In order to separate these variables, we use a physical phenomenon discovered in our lab, called the iso-path length (IPL) point. The IPL point is a specific angle around a cylindrical media, where the light intensity is not affected by the scattering and can serve for self-calibration. For a practical use of this concept, we designed an optic biosensor for measuring physiological parameters such as blood pressure, extracted directly from the absorption.

[TI-11] PIBM2024-0728-7

Integrated effects of far infrared therapy and aerobic exercise on sleep quality of female college students

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Abstract: Poor sleep quality is a significant public health concern. This study aimed to compare the integrated effects of aerobic exercise and far-infrared therapy on sleep quality in female college students with sleep problems. An electronic questionnaire was distributed among female college students at a university in Guangzhou, and 28 subjects with a Pittsburgh Sleep Quality Index (PSQI) score of 7 or higher were recruited. The subjects were divided into three groups using isometric sampling: Control group (Group C, n = 8), Aerobic Exercise group (Group A, n = 10), and Far-Infrared Therapy group (Group F, n = 10). Group C maintained their original lifestyle without any intervention, Group A underwent aerobic jogging for 8 weeks, and Group F underwent far-infrared sauna intervention for 8 weeks. Sleep quality was assessed using the 27 parameters of the PSQI before and after the interventions. P values can not differentiate the one group from the other groups. We introduced the geometric mean method to integrate all the PSQI parameters of a student. For each measurement, the geometric mean of the 27 parameters was termed the golden center (GC). The GC was found to be conserved: with improving health, positive or TCM Yang parameters increase while negative or TCM Yin parameters decrease, balancing to maintain the GC conservation. If the GC is conserved, the geometric mean of the reciprocals of all Yin parameters combined with all Yang parameters defines the geotime of the student. In terms of quantitative difference, the geotime of five students among eight students in group C decreased very significantly, but the one of six students among ten students in groups A or F increased very significantly. This is the first study to demonstrate the integrated impact of aerobic exercise or far-infrared therapy on sleep quality in female college students.

Binary Timon Cheng-Yi Liu

Professor

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Professor in School of Sports Science and Physical Education in South China Normal University, President of International Society for Complexity Science, Medicine and Engineering, Vice president of Guangdong Society of Physiology, Board member of Photobiomodul Photomed Laser Surg. Main interest is on the conservation paradigm and its applications in complexity science, medicine and engineering.

[TI-12] PIBM2024-0731-50

Autofluorescence lifetime imaging technology for tumor diagnosis

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Abstract: The global annual death toll from cancer exceeds 10 million, posing a severe threat to human health. There is an urgent need to develop non-invasive, highly sensitive and specific rapid screening and diagnostic technologies for early cancer detection or to assist surgeons in determining the safe margin during surgery. Fluorescence lifetime microscopy (FLIM) is highly sensitive to microenvironmental and molecular changes and is regarded as a potential technology in cancer diagnosis. Here, we present several methods for different cancer types through autofluorescence lifetime imaging and machine learning.

[TI-13] PIBM2024-0814-3

Two-photon Photodynamic therapy and assessment of cancer prognosis

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Abstract: Photodynamic therapy (PDT) can ablate the targeted diseased cells or tissue using photosensitizer (PS) generate reactive oxygen species (ROS) once excited by the light with specific wavelength, while the PS remains benign in the absence of light excitation. As compared with traditional cancer treatments, PDT is featured with remarkable advantages including minimal invasiveness, low side effects, etc., making it a promising treatment strategy. It is worth to note that cancer prognosis is extremely indispensable and important, which could correctly estimate the success with treatment and chances of recovery as well as assist to make subsequent therapeutic schedule. Herein, two-photon excitation would be employed to excite PDT with improved penetration depth and therapy precision. Moreover, the cancer prognosis was assessed under two-photon excitation at cytological, sub-cytological, and molecular levels, respectively.

[TI-14] PIBM2024-0726-2

High Speed Photoacoustic Imaging and Applications

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Abstract: Photoacoustic imaging possesses the merits of both high optical contrast and large acoustic penetration. It is expected to play a more and more important role in both fundamental research and clinical applications, and has the potential to revolutionize the playground of tumor and cardiovascular disease management and treatment. In this talk, I will focus on how we improve the speed of photoacoustic imaging. I will start with conventional photoacoustic microscopy using point-by-point mechanical scanning. Then I will move on to fast optical scanning based on MEMS and polygon mirror devices. After that, I will introduce single pixel imaging method without the need of scanning. Combined with sparse sampling, the imaging speed can be improved by 20 times. Besides photoacoustic microscopy, we also built photoacoustic computed tomography system which uses an array of ultrasound transducers to sense the signals. Due to simultaneous acquisition of photoacoustic signals, PACT can acquire 100 frames of two-dimensional images in one second. We applied our technology and instrumentation to study tumor microenvironment and evolution of tumor, as well as to investigate the mechanism of neurovascular coupling in the brain. We also intraoperatively guided a biopsy needle with photoacoustic imaging to extract tissue samples from sentinel lymph node to monitor tumor metastasis status. Our technology has also been successfully translated to human imaging to diagnose vascular plaques and image periphery blood vessels, aiming at better management of diseases such as diabetic foot or varicosity.

Chengbo Liu

Professor

Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, China

Chengbo Liu is a Professor at Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences. He received his Ph.D and Bachelor degrees from Xi'an Jiaotong University, each in 2012 in Biophysics and 2007 in Biomedical Engineering. His research interest focuses on multi-scale photoacoustic imaging instrumentation and translation. His team has published more than 100 journal papers, and been granted 23 patents. He is currently a senior member of OSA, SPIE and IEEE. He also serves as an editorial board member of Photoacoustics journal. His research has been funded with more than 10 grants including 6 grants from NSFC and MOST of China.

[TI-15] PIBM2024-0820-9

Identification and risk assessment of atherosclerotic plaques based on IVOCT

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Abstract: Vulnerable plaque rupture caused by atherosclerosis has seriously endangered human health. Intravascular optical coherence tomography (IVOCT) has become the main means of identifying vulnerable coronary plaque due to its high resolution. But image interpretation is time-consuming and labor-intensive, relying on the experience of clinicians. At present, research based on traditional machine learning has achieved classification of single frame images, but this information is not sufficient to assist clinicians in determining treatment plans and requires secondary judgement. This work proposes an evaluation algorithm for vulnerable plaque identification in IVOCT images based on an improved Faster-RCNN network framework. The network is generally divided into four parts: feature extraction, region extraction, secondary detection, and A-scan classification, so that it can locate vulnerable plaques with higher accuracy. The angle of accumulation of the lesion, the thickness of the fibrous cap, macrophage infiltration, superficial microcalcification, and vascular stenosis of vulnerable plaques are selected as indicators to assess the risk of rupture. The vascular lumen area is used to characterize the degree of vascular stenosis in vulnerable plaques, the smaller the lumen area, the more serious the stenosis. Furthermore, an adaptive threshold method is designed to calculate the thickness of the fibrous cap, which is considered as thin fiber cap when the thickness of the fiber cap is less than 65μm. The risk of plaque rupture was indicated with a lesion accumulation angle greater than 90°. The comprehensive application of these methods makes our work more comprehensive and accurate to play an important role in improving the efficiency and precision of the diagnosis of vulnerable plaques.

Qin Li

Professor

Beijing Institute of Technology, China

Li, Qin, Ph.D., is a professor of School of Medical Technology, Beijing Institute of Technology. She awarded the title of New Century Excellent Talents in University, Ministry of Education of China in 2008 and invited to be a member of the Biomedical Engineering Teaching Guidance Committee of the Ministry of Education. The main research fields are miniaturized technology of medical instruments, medical image processing, and the detection and processing of weak signal of biological specimen. Li Qin got the support from many grants, such as 863 Project, and Natural Scientific Foundation of China. And she has published more 120 papers related with her research fields.

[TI-16] PIBM2024-0730-10

Synchronous angio-lymphography based on photothermal induced resonance enhanced speckle variance OCT

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Abstract: In this paper, a new effect called the resonance enhanced speckle variance induced by photothermal effect (PTRESV) was introduced. The physical mechanism of the resonance enhanced effect was studied theoretically and experimentally, and the related theoretical model was established. Using this effect combined with photothermal modulated speckle optical coherence tomography (PTSV-OCT), a new photothermal induced resonance enhanced speckle variance OCT (PTRESV-OCT) imaging method with high sensitivity and "velocity screening" function has been developed. The experimental results show that when the modulation frequency of the pump light and the flow rate of the sample meet certain conditions, the speckle signal of the flow rate will produce significantly enhanced resonance phenomenon, and the resonance frequency is closely related to the modulation frequency of the pump light and the flow rate of the sample. The resonance enhanced speckle signal can effectively improve the detection sensitivity of PTSV-OCT, so as to realize the detection of tumor cells in lymphatic vessels in mice. The "speed screening" function of the resonance enhanced speckle effect can be used to selectively enhance the speckle signal of blood drug, so as to significantly improve the detection sensitivity of blood drug concentration, and provide a new technical means for the measurement of blood drug concentration in vivo.

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South China Normal University, China

Tang Zhilie, Professor of the School of Physics, South China Normal University. His research interests include photoacoustic/photothermal tomography, photothermal optical coherence tomography (PT-OCT) and confocal microscopy. He has completed many important scientific research projects such as National High Technology Research and Development Program of China (863 Program), the National Natural Science Foundation of China. And he has published more than 190 papers in important journals such as Nature Nanotechnology，Nature Communication, Optics Letters, Optics Express, Biomedical Optics Express, Chinese Science Bulletin, Science in China，etc. He has won the second prize of the National Teaching Achievement Award and the Guangdong Patent Award.

[TI-17] PIBM2024-0820-11

High Throughput Drug Screening based on ultrathin slicing, culturing, and label-free dynamic OCT detection

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Abstract: Rapidly screening effective drugs in cancer treatment is crucial for targeted therapy and precision medicine, holding broad social and economic benefits. To address this challenge, we have been developing a tumor drug screening platform based on fresh live sample slicing, culturing, and label-free detection. With ultrathin slicing using a custom-built vibratome, about a hundred tumor tissue slices were acquired from the fresh tumor sample, which were cultured and tested with different anti-cancer medicines. Further, we developed a dynamic OCT technique to quantify the cell dynamics, which provides a measure of the effectiveness of the medicine. In this presentation, we will introduce our latest progress and findings during the development of the high throughput drug screening platform.

[TI-18] PIBM2024-0728-6

Rational Manipulation of Excited-States Dynamics in Organic Materials for optimized photodynamic therapy

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Abstract: The dynamics of excited states in organic photosensitizers fundamentally determines the performance of clinical photodynamic therapy (PDT). Therefore, it is essential to deepen our understanding of the structure-dynamics relationship with aiming to manipulate excited states accordingly. However, the limited knowledge of excited-state dynamics in organic structures poses significant challenges to such rational manipulations. Our research addresses this gap by focusing on the structure-dynamics relationship in organic materials to enhance PDT performance. We utilized femtosecond transient absorption (fs-TA) spectroscopy to gain valuable insights into excited-state dynamics. Our research on excited-state dynamics in organic molecules revealed that geometry-twisting greatly enhances intersystem crossing (ISC), providing a new way to develop organic materials with external stimuli-responsive reversible switching of ISC. This understanding of ISC can lead to the development of advanced photosensitizers for PDT.

Wenbo Hu

Professor

Northwestern Polytechnical University, China

Wenbo Hu **i**s a professor at Northwestern Polytechnical University. He received his Ph.D. from Nanjing University of Posts and Telecommunications in 2016. From 2017 to 2019, he conducted postdoctoral research at the State University of New York at Buffalo. In 2020, he was appointed as a full professor at Northwestern Polytechnical University. His research specializes in the ultrafast excited-state dynamics of organic phototheranostic materials.

[TI-19] PIBM2024-0927-1

QPI techniques in combination with FLIM provide an extended set of data on cell response to external stimuli

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Abstract: An extended family of phase-sensitive techniques combined under the name Quantitative phase imaging (QPI) became a powerful nondestructive methodology in research of cells and tissues. QPI does not require any exogenous labels and utilizes low-power radiation. The traditional QPI techniques, off-axis digital holographic microscopy (DHM) and tomography (DHT), operate with coherent radiation and the results obtained suffer from errors caused by coherent noise. Recently the low-coherent inline QPI techniques, spatial light interference microscopy (SLIM) and transport of intensity equation (TIE), proved to be promising for application in biomedical research. Besides elimination of coherent noise, these techniques allow for connection to the inverted biological microscope and for combined fluorescent and FLIM measurements. In this report we consider advantages and disadvantages of the QPI methods on a particular example of the analysis of the response of cell samples in vitro to photodynamic treatment. The treatment of cell samples of the established cell lines was performed with the clinically approved chlorin-based photosensitizer Radachlorin. The post-treatment monitoring of samples using QPI provided data on changes in phase shift distributions and allowed retrieving information on the dynamics of a set of morphological and optical parameters of cells. The data obtained allowed us to distinguish between the three basic cell death pathways (apoptosis, secondary necrosis and necrosis) and to analyze cell response at the levels of both individual cells and cell ensembles. The in-parallel measurements of the same samples by FLIM provided an additional set of data on the post-treatment dynamics of photosensitizer fluorescence. The combined technique can also be used for analysis of both changes in cell morphology and variations in autofluorescence of metabolic coenzymes NAD(P)H and FAD in the course of cell death caused by external stimuli.

[TI-20] PIBM2024-0731-13

Semiconducting Polymer Dots for Photocatalytic Hydrogen Therapy

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Abstract: Hydrogen as a therapeutic agent has attracted a great deal of attention because of its superior therapeutic outcome on many diseases, including inflammatory injury, tumors, metabolic disorders, and neurological diseases. Photocatalytic hydrogen evolution is emerging as a promising strategy for hydrogen production and delivery. Here, we present a liposome-based nanoreactor platform which consists of heterojunction Pdots as a photocatalyst for diabetic wound healing. Under red light irradiation, the heterojunction Pdots lead to remarkable H_2 generation, effectively scavenging hydroxyl radicals and suppressing the expression of pro-inflammatory cytokines, thereby accelerating the healing of skin wounds in diabetic mice. Compared to single-component Pdots, the antioxidant capacity of the heterojunction Pdots in this work is ~10 times higher than that of the single-component Pdots in previous report. The red light is more biocompatible and can have better penetration depth than UV and blue light for *in vivo* anti-inflammatory applications. The anti-inflammatory properties of the Lipo-Pdots nanoreactors were evaluated in cellular assays and mouse models with lipopolysaccharide (LPS) induced inflammation. Cellular and subcutaneous ROS levels were effectively suppressed with a low light dose (~60 J/cm^2), about 3 to 10 times lower than those used for photodynamic therapy. Diabetic mouse model was established by an intraperitoneal injection of streptozotocin (STZ) that can damage pancreatic β-cells. Hydrogen therapy enabled by Lipo-Pdots inhibits the expression of pro-inflammatory cytokines and reduces the wound inflammation in diabetic mice, therefore promoting skin regeneration under a total light dose of 360 J/cm^2. This strategy provides a feasible approach by combining organic polymer dots and red light irradiation for safe and effective management of diabetic wound healing.

Changfeng Wu

Professor

Southern University of Science and Technology, China

Changfeng Wu completed his Physics PhD in 2004 at Institute of Optics, Fine Mechanics, and Physics, Chinese Academy of Sciences. He earned his PhD in Chemistry at the group of Prof. Jason McNeill from Clemson University in 2008. He then carried out postdoctoral research with Prof. Daniel T. Chiu at University of Washington. He started his group at Jilin University in 2012, and joined the faculty in Department of Biomedical Engineering at Southern University of Science and Technology in 2016. His research is focused on the development of optical probes, biosensors, spectroscopic and imaging techniques for biomedical applications.

[TI-21] PIBM2024-0727-4

Fluorescent probes for surgery navigation

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Abstract: Fluorescent probes play a key role in surgical navigation and become indispensable tools in modern surgical procedures, which provide real-time visual information during surgery, assisting surgeons in accurately locating the lesion or targe, tissue boundaries, and assessing the extent of pathologies. Especially, the ICG fluorescence imaging for surgery navigation (including sentinel lymph node imaging and dissection, hepatocellular carcinoma imaging and functional imaging). The clinical available fluorescent probes and laparoscope systems are in visible or NIR-I light region with low penetration depth or high background signal. Next, some NIR-II fluorescence probes for imaging and surgery navigation will be showed. Some difficulties of NIR-II fluorescent surgery navigation for clinical translation will be summarized. Thus, there is an urgent need to develop new endoscopic equipment and probes in NIR-II imaging window, and more consistent animal models to provide reliable evidence for preclinical studies. Overall, the development of novel fluorescent probes offers a new perspective for surgical procedures.

[TI-22] PIBM2024-0820-24

Custom ultrasonic detectors in biomedical photoacoustic diagnostics

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Abstract: Biomedical optoacoustic diagnostics combine the molecular specificity of optical methods with the depth and spatial resolution of ultrasound [1]. The angiographic capabilities of optoacoustic diagnostics—namely, the ability to visualize blood vessels of various calibers—are largely determined by the sensitivity and bandwidth of the ultrasonic antennas used [2]. Recent advancements in developing compact (<1 gram [3]), highly sensitive (<1 Pascal [4]) ultrasonic antennas with a wide angular coverage (over 90 degrees [5]) allow for the acquisition of high-quality angiographic images in both clinical and preclinical studies. This presentation will discuss the capabilities of broadband (0.3-30 MHz) non-invasive optoacoustic microangiography in detecting the remodeling of the deep vascular system in experimental tumors during radiotherapy [6], as well as the potential of clinical scanning optoacoustic angiography in diagnosing angiopathies [7]. The presentation will also cover future research directions, including the prospects of using multi-element piezopolymer (PVDF-TrFE) ultrasonic detectors in real-time optoacoustic cerebrovascular tomography.

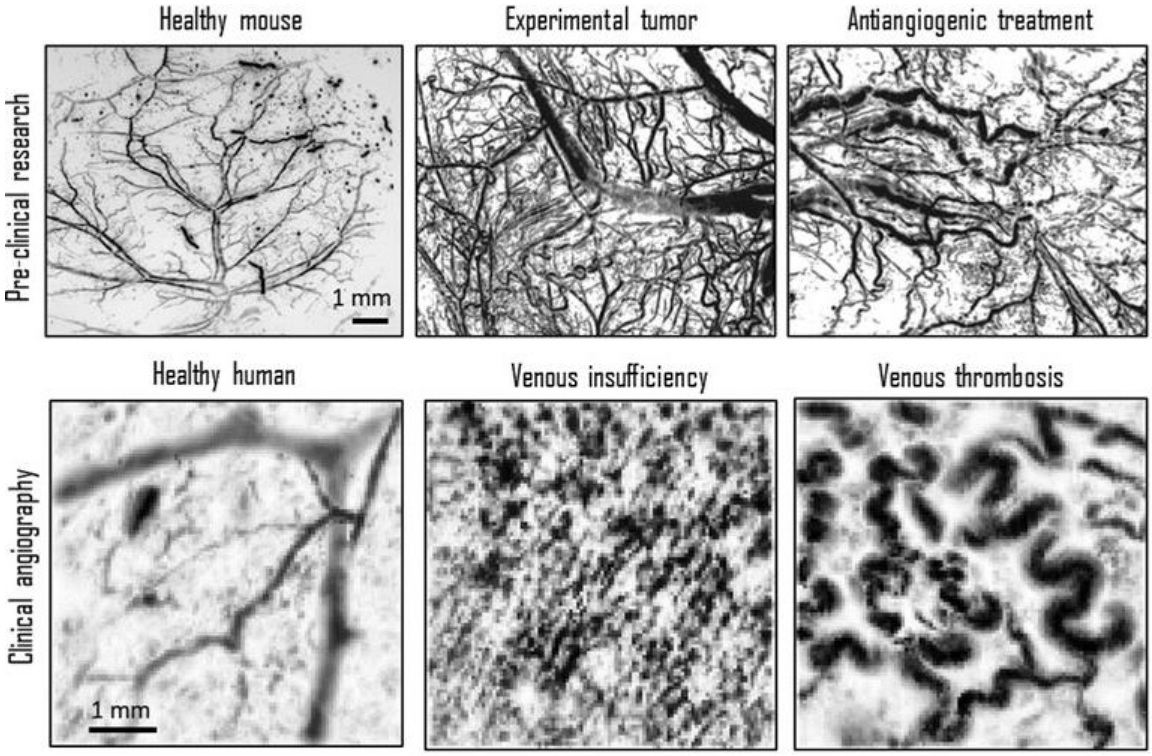

Figure 1: Wideband photoacoustic angiography for clinical and preclinical angiography.

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[TI-23]

Construction and Application of Organoids for Host-Pathogen Interaction Study and Drug Development

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Abstract: Research on host-pathogen interactions is an important direction in the field of microbiology, which has a wide range of theoretical and practical application significance in medicine, public health, and biosecurity. For a long time, in the study of host-pathogen interactions, providing a model that can reflect the actual situation in the host has been a significant difficulty in related research and application translation. Organoids are three-dimensional "micro-organ" systems that represent the structure and function of organs in vivo and have cell types, morphological distribution, and corresponding functions that are highly similar to those of corresponding organs in vivo. Organoids can not only provide a microenvironment that is highly close to the susceptibility, host response, physiological function, and multicellular linkage of the corresponding organs, but also have the advantages of simple operation, high throughput, no species differences, real-time monitoring, and diverse detection methods, so they have attracted much attention in the study of infection and immune mechanisms, as well as clinical application and drug development, and have also attracted more and more researchers and pharmaceutical industry R&D workers to study and apply them in multiple directions. The reporter has long been engaged in the development of organoids and organ-on-a-chip systems, including human airways, lungs, liver, bile ducts, intestines, blood vessels, kidneys, brain, etc., and has carried out multi-organ linkage for the study of infection immunity mechanism and drug development. This report will focus on the research progress and experience of developing and applying organoids for the study of host-pathogen interactions, demonstrate the exploratory application of organoids as an emerging host model in related research, and look forward to its possible potential for pharmaceutical R&D and translational applications in the future.

[CRI-1]

Spatial-temporal modulation superresolution optical imaging

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Abstract: Stimulated Emission Depletion (STED) microscopy is a highly effective optical super-resolution imaging technique. This technique surpasses the diffraction limit of resolution by introducing a depletion beam to suppress the emission of fluorescence. Since its proposal in 1994, STED technology has continuously evolved and improved. Its application in fields such as biomedicine and materials science has accelerated the rapid development in these areas. However, one drawback of STED is the requirement for high-power depletion light, which can potentially cause damage and phototoxicity to samples. To address this issue, we have developed strategies based on optical methods and fluorescent probes in recent years, aiming to reduce the required power of the depletion light while enhancing STED imaging performance, making it suitable for live-cell and even in vivo imaging. Since the working principle of STED relies on stimulated emission effects, to further reduce the required laser power and simplify the super-resolution imaging system, we proposed a fluorescence spatiotemporal modulation strategy based on phase analysis, built on time-resolved detection and computational imaging technology. This strategy combines temporal electronics with phase analysis methods, allowing for the acquisition of detailed and precise photon information from both temporal and spatial dimensions. Even using a single pulse laser as the light source, multicolor super-resolution imaging of live cells can be achieved.

[CRI-2] PIBM2024-0520-1

Future Technologies in Biophotonics: Photo-Therapy of Brain Diseases During Sleep

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Abstract: In modern neurobiology, sleep is considered as a novel biomarker and a promising therapeutic target for brain diseases. This is due to recent discoveries of the nighttime activation of the brain's drainage system (BDS) playing an important role in removal wastes and toxins from the brain and contributing neuroprotection of the central nervous system. We demonstrate pioneering and promising results suggesting that transcranial photostimulation (tPBM) during deep sleep stimulates more effectively lymphatic removal of amyloid-beta from the mouse brain than tPBM during wakefulness that associated with a greater improvement of the neurological status and memory of 5xFAD animals with Alzheimer's diseases. We discovered that tPBM stimulates the lymphatic contractility and pumping promoting effective clearance of wastes and toxins from brain tissues. We show that tPBM activates lymphangiogenesis, which is other mechanism underlying tPBM-mediated stimulation of BDS.

Based on preclinical data, we developed the non-invasive and portable technology for tPBM under wireless EEG-control of sleep to remove toxins from human brain. The wireless controlled gadget includes a flexible organic LED source that is controlled directly via mobile application. The design autonomous LED source is capable to provide the required therapeutic dose of light radiation at certain region of patient's head without disturbance of sleeping patient. To minimize patients discomfort advanced materials like flexible organic LEDs was used.

This research was supported by RSF project No.23-75-30001.

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[CRI-3] PIBM2024-0911-1

Label-free fluorescence spectroscopy: novel fluorophores in the human body and clinical translation

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Abstract: Label-free fluorescence spectroscopy is a powerful tool for biomedical diagnostics. This approach is based on the signal from endogenous fluorophores such as NADH and flavins (metabolic imaging), bilirubin (liver disease), lipofuscin (oxidative processes), melanin (melanoma) etc. However, a number of organs and structures exhibit fluorescence signal, whose origin is unknown – e.g., atherosclerotic plaques, parathyroid gland, amyloids and some tumours. Here we will discuss a framework for prediction of optical properties of molecules in the human organism with machine learning approach and demonstrate how it helps in understanding fluorescence formation. The examples of clinical translation of fluorescence spectroscopy will be also presented, including NIR autofluorescence.

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Evgeny Shirshin obtained PhD degree in laser physics (2011) and Dr. Habil. degree in optics (2024) from Moscow State University. He is currently Assoc. Prof. at the Faculty of Physics, Moscow State University, and Coordinator of the Interdisciplinary Scientific and Educational School of Moscow University «Photonic and Quantum technologies. Digital medicine». His research interests include biomedical photonics and clinical biophotonics, surgery guidance, fluorescence spectroscopy and imaging, FLIM, multiphoton microscopy, optics of the human organism. He authored commercial technologies in biomedical diagnostics, authored >150 papers, including PNAS, Nature Communications, Angewandte Chemie, Advanced Materials; h-index 25.

[CRI-4]

Ergodic Optical Speckle Imaging of 3D Blood Flowmetry

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Abstract: Quantitative monitoring of three-dimensional blood flow perfusion of biological tissue holds tremendous value in analyzing the biophysical and physiological basis of early disease. Optical coherence tomography (OCT) has emerged as a promising tool for measuring blood flow dynamics in vivo, providing a quantitative assessment of blood flow velocities in a range of tissues and organs. Doppler OCT is a commonly used modality that can directly detect blood flow velocity by analyzing the frequency shift or phase difference of light scattered by moving red blood cells. Correlation-based OCT utilizes the dynamic scattering induced time-varying OCT signals to derive blood flow velocity from the correlation coefficient of multiple A-scans at the same or adjacent location or fitting the intensity autocorrelation function based on the dynamic light scattering (DLS) model. However, the axial velocity of Doppler OCT suffers from a low detection range due to the phase wrapping. The maximum transverse velocity of correlation-based OCT is limited by the temporal resolution of the system on the premise of high spatial resolution. Since the correlation time may be less than the maximum time lag that is needed to fit the autocorrelation curve in DLSOCT in case of fast blood flow, even for the dynamic signals of consecutive A-scans. Here, we presented the ergodic speckle contrast optical coherence tomography (ESCOCT) to quantitatively measure blood flow velocity with a high dynamic range without prior knowledge of the flow geometry by using a 100 kHz swept-source (SS) OCT. By utilizing the velocity profile of non-Newton fluid, 3D velocity measurements with a range of 0–80 mm/s, corresponding to the average cross-section velocities of 4–40 mm/s, were demonstrated. A blood flow velocity of 280 mm/s was detected in the mouse middle cerebral artery when observing the response of the blood flow photothrombosis, which proved the benefits of rapid blood flow measurement for fast hemodynamic assessment.

[CRI-5] PIBM2024-0823-2

Forces of erythrocytes aggregation and their interaction with endothelium and the effect of interferon alfa-2b: an *in vitro* study with optical tweezers

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Abstract: The main goal of this work was to study *in vitro* the adhesion of erythrocytes to the endothelium, as well as the effect of endothelium on erythrocyte aggregation at various concentrations of interferon alfa-2b (IFNa) at its incubation with endothelium or its simple addition to the sample. Human umbilical vein endothelial cells were grown on round glass coverslips as a monolayer. Between measurements, the cells were kept in a CO_2 environment at 37°C. Whole blood was collected from the antecubital veins of healthy volunteers into lithium heparin tubes. The measurements were performed in microcuvettes with a monolayer of endothelium at the bottom, filled with plasma with a small number of erythrocytes (hct about 0.05%). Home built dual-channel optical tweezers using Nd:YAG laser (1064 nm, 100 mW) were applied for measuring the cells interaction forces in the piconewton range. The obtained results show a statistically significant decrease in paired erythrocytes aggregation forces in the presence of endothelium and IFNa. The magnitude of the effect is greater in the samples in which IFNa was added to the plasma without prior incubation with endothelium cells. In contrast, the samples, in which endothelium was incubated with IFNa for 24 hours and then exposed to plasma without IFNa showed weaker trends in reducing erythrocytes aggregation. The adhesion force of erythrocytes to endothelium was in the range of 1-2 pN in almost all experiments. This force decreased slightly or did not significantly change with increasing IFNa concentration. These results may support the hypothesis of a short-term effect of IFNa on the endothelial and erythrocyte system. Subsequent studies of the interaction of erythrocytes, endothelial cells and IFNa may clarify the mechanisms responsible for this interaction. The work was financially supported by the RSF grant #22-15-00120.

[CRI-6] PIBM2024-0823-1

Pitfalls in optical clearing agents induced enhancement of blood microcirculation imaging

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Abstract: The optical clearing agents (OCA) are used to improve the visualization of blood capillaries in the skin and blood microcirculation assessment with speckle contract imaging. Digital capillaroscopy (DC) is a method widely used for visualization of human capillaries in vivo, in particular, the nail bed capillaries. However, OCA being applied to the tissue surface can penetrate to the bloodstream. Most of OCA are osmotically active. They can change the microrheological properties of blood and locally alter the diagnosed blood flow, introducing errors in measurements using DC. The goal of this work was to demonstrate the possible effect of OCA blood microcirculation parameters as well as to find the ways to minimize such effect without giving up the optical clearing (OC). For this reason, we examined the efficiency of 15 different OCAs. The effect of OC was assessed using the OCT on the nail bed area of volunteers' finger after the application of OCAs. The effect of OCAs on RBC aggregation and deformability properties *in vitro* was measured by diffuse light scattering method. We showed that these properties of RBC dramatically changed when blood was incubated with OCAs. We also showed that the most effective OCA for enhancing the quality of blood capillaries imaging by DC technique is glycerol. We demonstrated that the capillary blood flow velocities measured by capillaroscopy of the nail bed depend on the type of OCA used to visualize the capillaries. We hypothesize that the mechanism for the observed differences is most likely that the OCAs penetrate into the capillaries and change the properties of the vessel walls and RBC. The capabilities of OC to improve the visualization of capillary blood flow and necessity to correct the parameters measured using DC are discussed. This work was supported by the RSF grant No. 23-45-00027.

Oral Presentations

Analytical Biophotonics

[AO-1] PIBM2024-0730-6

Photodynamic Mechanism of the Metal Nitrosyl Complexes and Their Interaction with Proteins

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Abstract: Nitric oxide (NO) as an important signaling molecule plays key roles in regulating blood pressure, the nervous system, immune responses, cellular apoptosis and viral infections. Metal nitrosyl complexes are one of promising candidates for the physiologically targeted delivery of NO. In this work, the photo induced NO release based on Ru and Fe complexes were investigated. The photodynamic mechanism for metal nitrosyl complexes were explored using time-resolved infrared spectroscopy (FT-IR) and electron paramagnetic resonance spectroscopy (EPR) in solution, and the photo induced NO release was successfully imaged in living cells using a NO selective fluorescent probe. Moreover, the interaction mode and molecular recognition with human Ferritin and human serum albumin were analyzed with fluorescence spectroscopy, their complex structures were determined. The nano-delivery system for good biocompatibility were developed. The study provides insight into potential biomedical applications for the metal nitrosyl complexes.

[AO-2] PIBM2024-0928-1

Structured Illuminations in Biomedical Microscopy with Diffractive Optics

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Abstract: By shaping laser beams in biomedical microscopes, structured illumination enhances performance for biomedical detection. Our diffractive-optics-based structured illumination microscopy uses diffractive optical elements (DOEs) for deeper, faster, and more precise imaging. This allows for high spatiotemporal resolution three-dimensional (3D) in vivo microscopy and ultra-high throughput multi-parameter single-cell imaging. Two notable examples developed by our team are the imaging flow cytometer (iFCM) and a needle-shaped beam (NB) for extended-depth-of-focus.

We developed a spectral imaging flow cytometer that profiles 5,000 cells per second in terms of molecular composition and morphology. This technology generates label-free scattering images and 32/64-channel fluorescence images of each cell. Innovations include the linear-array-spot-excitation (LASE) imaging method using DOEs, microfluidic chips for high-speed 3D hydrodynamic focusing, a MEMS sorter utilizing spark cavitation single bubbles, and a high-speed, high-sensitivity fluorescence spectrometer. This system can analyze 1 million cells every three minutes, aiding cell atlas creation, drug discovery, blood analysis, synthetic biology, cell and gene therapy, liquid biopsy, molecular breeding, and marine biology.

To address the trade-off between high resolution and deep depth of field in biomedical microscopy, we developed a needle-shaped beam (NB). This method extends the beam length by 83 times and improves 3D imaging efficiency in biological samples by 14 times compared to conventional Gaussian beams. The theoretical model uses a random spatial multiplexing strategy to convert the input beam into hundreds of axial foci, allowing for precise control over focal depth, beam diameter, spatial position, segment number, and energy distribution while suppressing sidelobe noise. We also developed fabrication protocols for 4-inch quartz wafer DOEs with 5nm precision and created metasurfaces containing 100 million nanocolumns using photolithography. The NB has broad applications in biomedical microscopy, including NB optical coherence tomography (NB-OCT) for skin cancer diagnosis, NB photoacoustic tomography (NB-PAT) for histology and angiography, and NB two-photon (NB-2P) for observing brain neuron activities.

[AO-3] PIBM2024-0730-37

Transient stimulated Raman scattering spectroscopy and imaging

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Abstract: Stimulated Raman scattering (SRS) has been developed as an essential quantitative contrast for chemical imaging in recent years. However, while spectral lines near the natural linewidth limit can be routinely achieved by state-of-the-art spontaneous Raman microscopes, spectral broadening is inevitable for current mainstream SRS imaging methods. This is because those SRS signals are all measured in the frequency domain. There is a compromise between sensitivity and spectral resolution: as the nonlinear process benefits from pulsed excitations, the fundamental time-energy uncertainty limits the spectral resolution. Besides, the spectral range and acquisition speed are mutually restricted. In this talk, we will introduce a novel time-domain excitation strategy that bypasses all these fundamental conjugations. We encoded the vibrational oscillations in the fluorescence signal or stimulated Raman loss (SRL) signal by femtosecond pulse-pair sequence excited vibrational wave packet interference. The Raman spectrum was then achieved by Fourier transform of the time-domain signals, which features the natural-linewidth-limit spectral line shapes, laser-bandwidth-determined spectral range, and improved sensitivity. Its advantages and drawbacks in biomedical imaging applications will be discussed in detail.

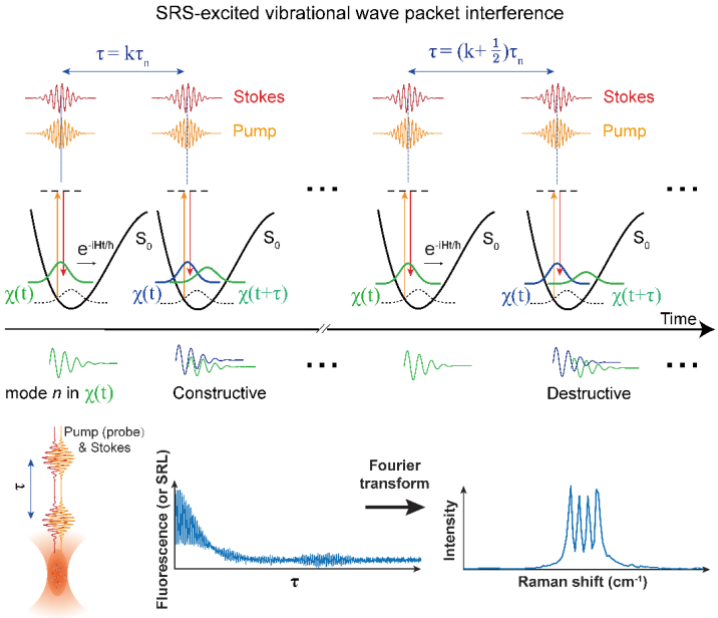

Figure 1: Principle of transient stimulated Raman spectroscopy.

[AO-4] PIBM2024-0731-9

Quality evaluation of Traditional Chinese Medicine based on Raman technology

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Abstract: It is of great scientific and practical significance to fully understand the connotation of Traditional Chinese medicine's (TCM) property, analyze the constituent devoting to its pharmacological effects, and establish a quality evaluation system accordingly. However, current research should be improved to meet the information loading, efficacy representativeness, and model accuracy requirement of TCM research. For this reason, in the work, Raman spectroscopy combined with deep learning was used to establish a quantitative analysis model for estimate the quality of TCM. As *Lonicera japonica* Thunberg (Jin Yinhua, JYH) for a present, Chlorogenic acid and total flavonoids were identified as the analysis targets. Then, combined HPLC, UV, and Raman Spectroscopy, the multi-source fingerprints spectra of JYH were obtained. Under the supervision of standard spectra, quantitative models were built based on Raman spectra by machine learning and deep learning methods. Among them, one-dimensional Convolutional Neural Network (1D-CNN) model showed superior prediction capability for simpler processing data, higher accuracy (R^2 = 0.9714), lower RMSE (0.001) and better data toleration. Moreover, coherent Raman scattering microscopy combined with *in vitro* anti-

inflammatory factor analysis were utility to established a high-throughput TCM efficacy characteristics. Dynamic changes of proteins and lipids were determined at laser pump light wavelengths of 2956 cm^{-1} and 2856 cm^{-1}, respectively. This method could be applied to both natural derivate compound and extracts with anti-inflammatory activity. In conclusion, this work would help to elucidate the scientific connotation of TCM, feasibly analyze the constituent, and provide technical support for its quality evaluation.

[AO-5] PIBM2024-0809-1

Rapid volumetric Raman imaging by integrating light-field scheme

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Abstract: Volumetric imaging enables visualization of three-dimensional (3D) structures of biological systems from the entire volume, providing significant value to brain function, developmental biology, and cell metabolism. Currently, volumetric imaging primarily utilizes fluorescence microscopy, but it lacks chemical composition information and relies on fluorescent labeling, which may cause issues such as cytotoxicity and photobleaching. In contrast, Raman microscopy provides unique fingerprint information of the distribution of samples in a label-free manner, showcasing the advantages of nondestructive and high specificity. Consequently, it is widely used in biomedical research and other fields. However, current techniques, the spontaneous Raman scattering-based confocal and light-sheet microscopies, are constrained by the inherent limitations of small Raman scattering cross-sections and weak signals. They often require tradeoffs among parallelization, resolution, and phototoxicity. The coherent Raman scattering has the advantages of fast imaging speed and high resolution, but the expensive equipment limits its application in biomedical research. In this paper, we propose a fast wide-field volumetric Raman imaging that integrates light-field technology. Combining light-field technology and wide-field Raman microscopic imaging technology enables the capture of distribution and components of samples in a single snapshot with a micro-lens array. Moreover, given the problems of resolution and artifacts existing in traditional reconstruction algorithms, we further develop a multi-stage data prior guidance-based fast high-resolution light-field algorithm, which enables fast and high-quality 3D reconstruction of samples with lateral and axial resolutions of approximately 2.71 μm and 3.64 μm, respectively. These experimental results demonstrate that this technique can accomplish the spatial distribution of biochemical components of zebrafish in a volume of 600 μm×600 μm×200 μm, which has great potential in rapid 3D imaging of biological samples.

[AO-6] PIBM2024-0820-7

Lightening the genome structure to understand its biological function

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Abstract: Spatial organization of the genome affects the interactions among regulatory elements and transcriptional outputs, and its abnormality is closely related to the development of a variety of congenital defects and cancers. Although the mis-folding of chromatin structures can alter the insulation between adjacent domains and thus affects expression of specific genes, it remains unclear whether the genome structure has a general role on transcriptional regulation. Here we developed 3D ATAC-PALM, a super-resolved imaging technique, to directly visualize accessible chromatin sites across the genome at the nanometer resolution within 3D nucleus. Our results have revealed clustered spatial distribution of accessible chromatin and uncovered novel factors underlying its structural regulation. Moreover, combining this imaging approach with high-throughput single-cell sequencing techniques, we have discovered that the 3D genome organization directly orchestrates genome-wide gene co-regulation and affects cross-domain gene co-expression, suggesting a previously unknown layer of gene regulation distinct from the classical one orchestrated by promoter-enhancer interactions. Taking together, our research has developed novel tools for genome structure measurement, revealed unexpected gene regulatory mode and might pave the way for deciphering the etiology of relevant diseases.

[AO-7] PIBM2024-0618-1

Rainbow light sheet illumination for snapshot 3D imaging

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Abstract: Traditional lens-based three-dimensional (3D) imaging methods struggle with speed, spatial resolution, field of view, and depth of field (DOF). Here we propose a volumetric imaging method that combines rainbow-sheet illumination, chromatic-aberration-induced DOF extension, and compressive hyperspectral imaging to optically section transparent objects over 200 depth slices in a single snapshot. A proof-of-concept mesoscopic system with a lateral resolution of 12.7 line pairs per millimeter and a depth resolution of roughly 140 microns in a volume of 10×10×10 millimeters is constructed. The practicality of the suggested method is demonstrated by dynamic volumetric imaging of a transparent jellyfish at a rate of 15 volumes per second.

[AO-8] PIBM2024-0819-5

Emission depletion super-resolution microscopy with upconversion nanoparticles

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Abstract: Nonlinear depletion of fluorescent states through stimulated emission constitutes the basis of far-field stimulated emission depletion (STED) microscopy. Despite significant efforts over the past decade, realization of sub-diffraction-limit resolution at low-saturation beam intensities through STED remains a major technical challenge. Here we report two novel strategies for achieving high-efficiency depletion of fluorescent states in lanthanide-doped upconversion nanoparticles. We call the first strategy as surface-migration emission depletion (SMED), in which the energy of fluorescent state is inhibited by the surface quenching effect on the crystal surface. Instead of causing a direct stimulated emission process, the depletion laser beam in this strategy only needs to guide the energy of emitting state to the nanocrystal surface, and the energy would be finally depleted by the surface quenchers. Based on this strategy, we achieved 95% depletion efficiency and a saturation intensity of 18.3 kW cm^{-2} for the blue emission of Tm^{3+}-activated nanoparticles, and this high-efficiency emission depletion enables the following super-resolution imaging with an average lateral resolution of 20-nm (depletion beam power: 4.85 mW). The second strategy, namely stimulated excitation depletion (STExD), is a general emission depletion method for various lanthanide ions. In the principle of STExD, the upconversion sensitizer-activator system is fully utilized. The stimulated emission process occurs in the sensitizer, which commonly shared by different luminescent ions. When the energy of sensitizer is inhibited, all different luminescent ions would not be able to harvest energy, in other words, the excitation is inhibited. In addition, we also observed an interesting cascade amplified depletion phenomenon in the operation of STExD. An ultra-high depletion efficiency of 99% was achieved for the three-photon blue emission of Nd^{3+} ion. With the STExD strategy, we achieved emission depletion phenomena in lanthanide ions such as Nd^{3+}, Er^{3+}, Ho^{3+}, Tm^{3+}, by only using one pair of fixed lasers, multicolor super-resolution imaging was demonstrated.

[AO-9] PIBM2024-0730-11

Single-pixel fluorescence imaging

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Abstract: Fluorescence imaging can dynamically monitor changes and transfers of fluorescent probes *in vivo* with a large field of view, so it has a wide range of functional biomedical applications, but it usually lacks structure (background) information leading localization difficulty. In this paper, we propose a single-pixel fusing imaging that can obtain matched fluorescence image and diffuse reflection image, so it can obtain structure and functional information simultaneously. Comprehensively considering dynamic range, wavelength response, volume, and cost, we conclude that SiPM is the most suitable detector in the proposed imaging. We then prove the imaging method and the detector by ample and animal experiments, so we can obtain

complementary background information to existing fluorescence imaging for colocalization. We hope this method can improve the fluorescence imaging and promote the application of single-pixel imaging and SiPM.

[AO-11] PIBM2024-0818-1

Exploration of the generalization and hallucination in deep learning: a study based on imaging through scattering medium

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Abstract: With fast developments of computational power and algorithms, deep learning has made breakthroughs and been applied in many fields. However, generalization remains to be a major challenge, and the limited generalization capability severely constrains applications of deep learning in practice. The hallucinations issue is another unresolved conundrum faced by deep learning and large models. By leveraging a physical model of imaging through scattering media, we studied the lack of generalization to datasets and system response functions in deep learning respectively, identified their causes, and proposed universal solutions. The research also provides an explanation for hallucinations. In general, it enhances the interpretability of deep learning from a physics-based perspective. It will pave a way for direct interaction between deep learning and the physical world, facilitating the transition of deep learning from a demo toy to a practical tool.

[AO-12] PIBM2024-0729-17

Diff-FMT: Diffusion Model for Fluorescence Molecular Tomography

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Abstract: Fluorescence molecular tomography (FMT) is a real-time, noninvasive optical imaging technique playing a pivotal role in biomedical research. Nevertheless, the ill-posed nature of the inverse problem presents significant challenges in image reconstruction. In previous studies, traditional iterative reconstruction methods suffer from long reconstruction times and low-quality images, while deep learning methods have shown tremendous potential, they are heavily reliant on large-scale, high-quality prior datasets. To address the aforementioned issues, we, for the first time, propose a FMT reconstruction method based on a denoising diffusion probabilistic model, termed Diff-FMT, which is capable of obtaining corresponding high-resolution reconstructed images from noisy images given any labeled image. The framework of Diff-FMT includes forward

diffusion, inverse process and sampling process. In the forward diffusion process, we gradually add noise to the reconstructed image, and at the same time store the generated noise image and its corresponding noise information to provide conditions for the inverse process. In the reverse process, to guide the learning of the noise prediction network, we incorporate the label image as conditional information into the training process, and this constraint can make the generated reconstructed image gradually close to the label image. In the sampling stage, we then use random noise images as initial images to gradually generate high-resolution FMT images given any label images. To evaluate the performance of Diff-FMT, we perform simulation experiments and compare it with other cutting-edge algorithms, and the experimental results show that the algorithm can achieve high-resolution fluorescence reconstruction images.

[AO-13] PIBM2024-0820-19

Light-efficient meso-SCAPE microscopy with multi-millimeter field-of-view and cellular resolution

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Abstract: Swept confocally-aligned planar excitation (SCAPE) microscopy, renowned for its open sample space and translation-free 3D imaging with high volumetric rate, proves highly valuable for both biological and neuroscience studies. To expand the field of view (FOV) towards the multi-millimeter scale requires the use of a low-mag primary objective; however, off-the-shelf objectives that can accommodate a ~5-mm-diameter FOV are usually limited in terms of numerical aperture (NA, typically no more than 0.5), which restricts the maximal tilting angle of the oblique illumination plane and eventually renders it extremely challenging for the tertiary objective to collect any decent percentage of the fluorescence signal. Existing work-arounds to increase the tilting angle of illumination plane entails either employing an extra synchronous galvanometer scanner (and sometimes even an extra illumination objective) to maintain the de-scan operation or introducing a grating into the beam path (in the focal region of either the primary or the secondary objective); the former is accompanied by complicated beam path and control electronics, while the latter leads to collection loss. We herein propose a novel single-galvo meso-SCAPE microscope that integrates an immersed reflector-based overly titled illumination light sheet and a single-galvanometer-based self-conjugated re-scan strategy that affords independently controlled beam steering angle for the excitation and detection beam paths. This newly-developed meso-SCAPE microscope accommodates an illumination plane tilting angle up to ~60 degree (with respect to the optical axis) and achieves a ~5-mm-diameter field-of-view, cellular resolution, high-efficiency de-scanned collection of epi-fluorescence, and a rapid volumetric imaging rate up to ~5 volume/s. We will present in the conference design principles as well as experimental demonstrations of high-speed volumetric visualization of structural and functional dynamics of live organisms.

[AO-14] PIBM2024-0930-3

Reflective Computational Light Sheet Microscopy

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Abstract: Light-sheet microscopy stands out as a powerful tool in biological imaging due to its exceptional performance in fluorescence imaging. However, achieving both high sectioning performance and a vast field of view (FOV) poses a fundamental challenge in conventional light-sheet microscopy. The light-sheet thickness is typically constrained to 1 μm for a wide FOV, potentially compromising resolution. To address this limitation, we introduce an axial scanning light-sheet microscopy (ASLM) technique integrated with aberration-free tunable foci to enable high-NA excitation while maintaining a generous FOV. The proposed scheme successfully achieves isotropic resolution of 280 nm in a three-dimensional imaging system, encompassing a FOV of 80 × 80 μm and an impressive imaging speed of 60 ms per frame. These remarkable characteristics underscore the immense potential of ASLM for high- spatiotemporal resolution imaging.

[AO-15] PIBM2024-0731-12

Algorithm-accelerated Six-dimensional WAXD Tensor Tomography

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Abstract: We propose a novel 6D X-ray wide-angle diffraction (WAXD) tensor tomography method which only requires a conventional 3D scanning tomography acquisition protocol. The new method can increase the acquisition efficiency of the 6D WAXD tensor tomography by at least one order of magnitude by fully exploring the hidden 3D reciprocal information in the 2D WAXD pattern.

X-ray scattering/diffraction tensor tomography techniques are promising methods that can acquire the 3D texture information of heterogeneous biological tissues at micrometer resolution. However, the methods suffer from a long overall acquisition time due to the multi-dimensional scanning across the real and reciprocal space. Here we introduce a new approach to obtain 3D reciprocal information of each illuminated scanning volume using mathematical modeling, which is equivalent to a physical scanning procedure for collecting full reciprocal information required for the voxel reconstruction. The virtual reciprocal scanning scheme was validated by a simulated 6D WAXD tomography experiment. The theoretical validation of our method represents an important technological advancement for the 6D diffraction tensor tomography and a crucial step toward pervasive applications in the characterization of heterogeneous materials.

[AO-16] PIBM2024-0730-14

Cardio-cerebrovascular organ-on-a-chip and its integration with AI

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Abstract: Organ-on-a-chip technology provides a powerful platform for drug discovery, physiological and pathological studies. Due to the nature of microfluidic channels, organ-on-a-chip has been widely utilized to faithfully mimic blood vessel systems. We have fabricated several different types of organ-on-a-chip platforms, which replicate the human blood-brain barrier (BBB) and human artery under different environments or conditions, including micro-gravity, Parkinson's disease and brain tumor. Based on these chips, we are able to evaluate different disease/condition intervention methods, and further explore the integration with artificial intelligence.

[AO-17] PIBM2024-0820-20

Quantitative Phase Imaging with Complex Amplitude Constrained Illumination

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Abstract: Quantitative phase imaging (QPI) has emerged as a powerful label-free technique for observing transparent samples in biomedical research. Traditional interferometer-free QPI methods often require axial movement of the detector, limiting acquisition speed and introducing errors. We present a novel QPI method based on complex amplitude constrained illumination to address these limitations. Our technique uses complex amplitude modulation to manipulate the illumination field, providing simultaneous amplitude and phase constraints. By varying the illumination's complex amplitude distribution, we obtain diffraction intensity images under different conditions without moving the detector, thus eliminating mechanical errors and enhancing stability. Our method accelerates the convergence of the iterative phase reconstruction algorithm by providing simultaneous amplitude and phase constraints, significantly reducing the number of required diffraction images. High-quality phase images are obtained with only three illumination switches, speeding up acquisition and minimizing potential sample damage. We constructed an experimental setup using a Digital Micromirror Device (DMD) to validate the proposed method, achieving a maximum complex amplitude constraint transformation rate of 17.8 kHz. Results demonstrate superior performance in imaging speed, reconstruction accuracy, and temporal resolution compared to traditional methods. This novel QPI technique offers a stable, high-speed, and accurate solution for quantitative phase imaging, providing researchers with a powerful tool for investigating cellular dynamics and structure. It opens new possibilities for non-invasive, high-resolution studies of living systems. Future work will extend the method to 3D phase tomography and explore its applications in various biological studies.

[AO-18] PIBM2024-1015-3

Noncontact elastic measurement using Laser profilometer with airpuff excitation

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Abstract: Elasticity is one of the fundamental properties of materials. It is not only an important diagnostic parameter to investigate physiological dysfunctions in biological tissues but also widely measured in industry. This paper present a novel method to accurately measure the elastic by Rayleigh wave tracing on the surface of phantoms using laser profilometer with airpuff excitation. The elastics of agar phantom with 0.6%, 0.8%, 1.2% and 1.5% concertation were measured. The method is validated by comparing it with the results obtained by using a laser speckle elastography. To the best of our knowledge, this is the first elastic modality based on laser profilometer. This method can to be used for online elasticity measurement of biological and industrial materials.

Immunophotonics

[IO-1] PIBM2024-0731-30

Single-cell multi-parametric simultaneous photoacoustic vasculography and lymphography *in vivo*

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Abstract: Blood vessels and lymphatic vessels are crucial components of the tissue microenvironment. Simultaneous imaging of both can provide more comprehensive information about the microenvironment, aiding in the understanding of physiological and pathological processes within tissues. For example, in tumor imaging, the growth and metastasis of tumors are closely related to blood vessels and lymphatic vessels. Tumors obtain nutrients and oxygen through blood vessels and metastasize through lymphatic vessels. Simultaneous imaging of both can reveal the mechanisms of tumor invasion and metastasis, offering new targets and strategies for tumor treatment. Here, we present a high-speed single-cell multi-parametric photoacoustic optical-resolution photoacoustic microscopy (OR-PAM) technique to realize simultaneous photoacoustic vasculography and lymphography *in vivo*. To achieve multi-functional imaging, a five-wavelength pulsed laser source is generated based on a 532-nm nanosecond pulsed laser and stimulated Raman scattering (SRS) shifters, which can acquire hemoglobin concentration, oxygen saturation, blood flow speed, and lymphatic concentration simultaneously. To achieve multi-morphological imaging, enhanced image processing methods are developed to obtain multi-morphological vessel evaluations of vessel density, vessel direction, vessel diameter, and vessel tortuosity. To achieve dynamic imaging, a fast scanner is combined with the five-wavelength pulsed laser source to improve the multi-spectral scanning speed. An exogenous agent is used in the mouse ear to differentiate the lymphatic and blood vessels. The SNR of blood and lymphatic vessels is measured to be greater than 20 dB. Based on this system, the dynamic processes of brain metabolic changes due to drugs, lymphatic clearance processes, and ischemia-reperfusion processes in the mouse ear are monitored and demonstrated. We believe this technique enables in vivo simultaneous multi-parametric vasculography and lymphography, which can be applied in further biomedical imaging fields.

[IO-2] PIBM2024-0830-1

Optical imaging of chlorotoxin-melittin nanodrug targeting and immunotherapy for glioma

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Abstract: Glioma is a common primary malignancy of the central nervous system. Several drugs have exhibited promising efficacy in killing glioma cells *in vitro*. However, given the immunosuppressive tumor microenvironment of the glioma and the impediment of the blood brain barrier (BBB), it is difficult for these drugs to cross the BBB and accumulate to the effective therapeutic concentration in the glioma regions of the brain. We developed a novel chlorotoxin-melittin nanoparticle (CTX-melittin-NP) and used several imaging technologies to demonstrate their ability to cross the BBB, target and kill the glioma cells, and remodel the immunosuppressive microenvironment of glioma into an immunoactivity type.

Firstly, we investigated that CTX-melittin-NP could target and kill GL261 in mouse glioma cells through in vitro co-incubation experiments and live-cell imaging. Then, the transwell experiment and confocal imaging confirmed that DiR-BOA-labeled CTX-melittin-NP uptake by microvascular endothelial cells (b.End 3) and transferred across the endothelial cells. Furthermore, it was observed by intravital imaging that CTX-melittin-NP could cross the BBB into the glioma area after intravenous injection for 20 min, and was engulfed by glioma cells and macrophages. Whole-body fluorescence imaging of the brain demonstrated that CTX-melittin-NP could effectively inhibit the growth of glioma with an inhibition rate of 94.9%. Immunofluorescence confocal imaging showed that the number of $CD3^+$ T cells, B cells and macrophages infiltrating into glioma was significantly increased after CTX-melittin-NP treatment, suggested that the CTX-melittin-NP reversed the immunosuppressive microenvironment to an immune-activating microenvironment. Thus, CTX-melittin-NP represents a promising nanodrug strategy for glioma immunotherapy.

[IO-3] PIBM2024-0820-12

Cell Organelle-Targeted Phototherapy Primes Checkpoint Blockade Immunotherapy

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Abstract: Although checkpoint blockade immunotherapy achieved great success in clinic in the past decade, the response rate of the monotherapy remains unsatisfying. Photodynamic therapy (PDT) and photothermal therapy (PTT) are reported to be immunogenic local treatments to cancer, but rarely elicit systemic immune response due to the suppressive tumor microenvironment. We report a few nanophotosensitizers targeting cell nuclei or mitochondria to cause cell organelle-specific damage upon light irradiation, inducing immunogenic cell death, thus synergizing with immune checkpoint blockade therapy. In bilateral tumor models, cell organelle-specific PDT/PTT in combination with anti-PD-1 not only eradicate light irradiated tumors, but also suppress the growth of distant tumors. We observed increased dendritic cell maturation after PDT/PTT and anti-PD-1 treatment, evidencing the enhanced antigen presentation. The significant increase of pro-inflammatory factors including IFN-γ, TNF-α and IL-6 in the serum also confirms the activation of systemic immune response. In the distant tumors in the combination treatment group, significantly enhanced CD8+ T cell infiltration was also detected. Therefore, we demonstrate the potential of cell organelle-targeted phototherapies in combination with checkpoint blockade immunotherapy on metastatic cancers.

[IO-4] PIBM2024-0730-21

Multi-scale visualization of the adjuvants dynamic transporting from cell to organ by photoacoustic imaging

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Abstract: Adjuvants are indispensable ingredients in vaccine formulations. In vivo evaluating the transport process of adjuvants from cell to organ with the same imaging method is a challenging task. Based on an unique principle, photoacoustic imaging combines the advantages of high resolution and great contrast of optical imaging, as well as the deep tomographic capability of acoustic imaging. In this study, the process of macrophage phagocytosis of adjuvants, the process of inhaled adjuvants crossing airway walls, and the transport of injectable adjuvants in the lymphatic system and muscles were characterized through photoacoustic imaging. In vivo imaging under the same optical labeling is highly beneficial for accurately evaluating the immune effects of adjuvants. Consequently, multi-scale photoacoustic imaging technology has great potential to accelerate the research process of new adjuvants.

[IO-5] PIBM2024-0722-2

Multimodal collaborative tumor precision therapy based on phototherapy

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Abstract: Chemotherapy, radiotherapy and surgery are the main treatments in the field of tumor therapy, but they all have their own limitations. Phototherapy, including photodynamic therapy (PDT) and photothermal therapy (PTT), which relies on the conversion of light energy into chemical and thermal energy by phototherapeutic moieties to kill tumors, has been widely used in clinic as a non-invasive oncologic therapeutic modality. Besides, the biological effects in vivo of phototherapy can be combined with other strategies to achieve the purpose of synergistic treatment. In this study, we constructed a nanobiomaterial drug carrying system for multimodal combined precision treatment of solid tumor, which combined immunotherapy, gene therapy, chemotherapy and phototherapy to make each treatment cooperative and enhance tumor treatment including effective inhibition of tumor development, metastasis and recurrence. In vitro and in vivo experiments have shown that these tactics may provide a promising and pragmatic platform for clinical applications.

[IO-6] PIBM2024-0510-1

Nanocomposite copper carriers regulating tumor cell copper homeostasis for synergistic antitumor studies of photothermal therapy and cuproptosis

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Abstract: Cuproptosis is an emerging mode of programmed cell death with great potential for clinical development in inducing tumor cell death and immune response. However, the special copper ion regulatory mechanisms in most tumor cells maintain intracellular copper ion homeostasis and against the occurrence of cuproptosis. Here, we developed a multifunctional Cu_9S_8-based nanoplatform (CAPSH) to precisely target breast tumor tissues, effectively enhance cuproptosis by ATP7A interfering, and integrate thermodynamic therapy with immune effects. Alkyl radical precursors 2,2'-azobis[2-(2-imidazolin-2-yl) propane] dihydrochloride AIPH was loaded into the hollow structure of Cu_9S_8 nanoplatform, coated with polyacrylamide hydrochloride (PAH) for the electrostatic adsorption of siRNA, and hyaluronic acid (HA) was encapsulated to protect the siRNA and enable targeted delivery. With deeper penetrating near-infrared light (wavelength: 1064 nm) irradiation, CAPSH pyrolysis released AIPH and copper ions, triggering photodynamic death and cuproptosis occurring in situ in breast tumors. At the same time, the release of SiRNA (SiATP7A) disrupted the copper homeostatic mechanism of tumor cells, significantly enhancing cuproptosis and following immunological effects. This nanoplatform simultaneously regulates cuproptosis from both principles of onset and development, facilitating the application of cuproptosis in tumor therapy.

Neurophotonics

[NO-1] PIBM2024-0731-41

High-throughput volumetric mapping of synaptic transmission

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Abstract: Two-photon fluorescence microscopy (2PFM) for in vivo recording of neuronal activity have significantly advanced our understanding of brain function. Whereas routine monitoring of cellular activity from thousands of neurons can be achieved by 2PFM, the number of synapses that has been imaged simultaneously in vivo is much smaller than total number of inputs received by a neuron. This problem becomes particularly challenging when one wants to map synaptic transmission using genetically encoded indicators such as iGluSnFRs. Targeted to membrane and with smaller transient magnitudes and faster dynamics than calcium indicators, glutamate sensors require the microscope to operate at high spatial and temporal resolution. Laterally confined and axially extended, when scanned in 2D, a Bessel beam can effectively probe the structures within a 3D volume. However, due to the presence of substantial side-ring two-photon fluorescence excitation, especially at high numerical aperture (NA), the Bessel foci used for calcium imaging has been limited to $\leqslant$0.4 NA. When applied to glutamate imaging, the relatively low NA of Bessel foci leads to dimmer signal thus insufficient SNR. Increasing the NA of Bessel foci leads to strong side-ring excitation that reduces image contrast. Here, we report a method of shaping the excitation wavefront to generate axially extended Bessel-droplet foci with substantially suppressed side rings. Using an interference-based approach for axial scanning, we could image continuous volumes at high-contrast, high-resolution volumetric up to 0.7 NA. We validated the performance of Bessel-droplet 2PFM in the challenging applications of volumetric glutamate imaging in the mouse primary visual cortex (V1). With Bessel-droplet 2PFM, we mapped glutamate transmission from >1,000 synapses per volume and found spatial organizations of visually evoked glutamate transients. In addition, our ability to image at high throughput enabled us to discover novel features in the spatial organization of glutamate transients.

[NO-2] PIBM2024-0820-6

Adaptive optics two-photon microscopy for longitudinal high-resolution imaging in deep tissues

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Abstract: Two-photon excitation fluorescence microscopy (TPEFM) is widely used for tissue imaging owing to its inherent optical sectioning capability and considerable penetration depth in tissues. However, visualizing biological processes at subcellular resolution without disrupting the natural microenvironment remain challenging, mainly due to optical aberrations and tissue scattering. We have developed adaptive optics (AO)

techniques for rapid measurement and correction of optical aberrations in biological tissues. After aberration correction, diffraction-limited resolution in deep tissues can be restored, enabling the observation of dynamic biological processes in a minimally invasive way. I will present the AO-TPEFM technique and its application to live imaging neuronal and glial cells in the central nervous system, including the retina, spinal cord, and brain.

[NO-3] PIBM2024-0802-1

Development of Tools and Algorithms for Mesoscopic All-Optical Closed-Loop Neuroscience Research in Deep Brain

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Abstract: Multiphoton microscopy is an indispensable tool in neuroscience research, widely used to record structural and functional of neural activities of the deep brain in living animals. With the advancement of various "Brain Initiatives" in recent years, cutting-edge neuroscience research urgently requires imaging and manipulation techniques with high spatiotemporal resolution at the mesoscopic scale. These techniques enable simultaneous studies at the molecular, neuron, neural ensemble, and multi-brain region levels to explore the synergistic interaction between brain regions and deepen our understanding of brain functions. This talk will introduce a newly designed multiphoton microscope and holographic optogenetic stimulation system. It will also cover an deep-learning based ultrafast denoising method achieving processing rates surpassing 1K FPS and an adaptive holographic optogenetic stimulation method developed based on this system. The introduction of these methods not only significantly enhances large field-of-view, high-speed, high-resolution imaging of deep tissues in living animals but also improves the precision and efficiency in manipulating neuronal activities. We envision these advancements will provide essential tools for mesoscopic all-optical closed-loop neuroscience research.

[NO-4] PIBM2024-0819-23

Pattern-modulated optoacoustic neurostimulation with nanocomposites microarrays for visual prostheses

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Abstract: Photoreceptor degeneration caused by retinitis pigmentosa (RP) or age-related macular degeneration (AMD) has long been a leading cause of blindness. Fortunately, although patients with retinal degeneration lose light sensitivity, the retinal ganglion cells and optic nerve still have some functionality, and the rest of the visual pathway is mostly intact and functional, which makes vision restoration possible. Ultrasound, as a medical imaging modality, can also serve as a viable non-invasive method for vision restoration. The photoacoustic effect is an alternative method for generating ultrasound waves. Compared to

piezoelectric-based ultrasound transducers, concave laser-generated ultrasound transducers can focus higher acoustic pressure at the focal point due to their self-focusing effect, offering higher resolution and broader bandwidth. We have successfully demonstrated repeated stimulation of neurons using a 500 μm single concave transducer. We designed a micro concave transducer array membrane composed of PDMS and carbon materials as a visual prosthesis, with single-element sizes smaller than 300 μm and a pixel count exceeding 400. Combined with an optical scanning device, this system enables programmable, patterned generation of highly focused ultrasound to match and transmit external patterns to the retina. These results demonstrate the potential of using laser-generated ultrasound transducers to stimulate damaged retinas and serve as retinal prostheses.

[NO-5] PIBM2024-0729-13

Concurrent imaging of burst firing neurons and vascular oxygen supply at high spatiotemporal resolution in the awake mouse brain

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Abstract: Neural activity in the brain relies on oxygen supply through cerebral blood microcirculation. Imaging of neurovascular coupling is essential for understanding mechanisms underlying brain functions and cerebral diseases. Yet, current imaging methods suffer from low spatiotemporal resolution to resolve specific coupling networks or lack functional blood oxygen metabolism information. Here, we show that a concurrent confocal fluorescence and photoacoustic microscopic technique mitigates these limitations and achieves imaging of concomitant firing of single neurons and vascular oxygen supply in the awake mouse brain. We demonstrate the capability of this technique by performing *in vivo* experiments involving anaesthesia and hypoxia challenges, as well as whisker and electrical stimulations of the mice. We established correlations among neuronal activity, blood vessel diameter and blood oxygen saturation. Our technique may allow to obtain a better understanding of the complex interplay between neurons and blood vessels in the brain and thus is a promising tool in the study of neurovascular coupling in health and disease.

[NO-6] PIBM2024-0731-27

Transcranial Ultrasound Neuromodulation Guided by Ultrasound Imaging

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Abstract: Ultrasound neuromodulation is an important method for studying neural circuits and treating neurological and psychiatric disorders, showing tremendous application prospects in the field of brain disease treatment. The visualization-guided navigation of low-intensity focused ultrasound stimulation beams and real-

time monitoring of neural activity are crucial for improving modulation efficiency and studying modulation mechanisms. Current ultrasound neuromodulation mainly uses MRI navigation, but its high cost, low portability, compatibility complexity with ultrasound, and low imaging time resolution hinder further development of this technology. Using ultrasound imaging-guided ultrasound neuro modulation can overcome these difficulties. To assess therapeutic beam pathways, this work combines passive beamforming technology with ultrasound imaging to visualize the focus position of low-intensity focused ultrasound stimulation. Through simulations, in vitro, ex vivo, and in vivo experiments, the estimated focus area is compared with the actual focus area induced by low-intensity focused ultrasound (modulation area), validating the feasibility of ultrasound imaging-guided transcranial ultrasound neuromodulation. Experimental results demonstrate that this technology is highly beneficial for guiding ultrasound neuromodulation, offering new ideas and methods for precise treatment of brain diseases and research into ultrasound brain modulation mechanisms.

[NO-7] PIBM2024-0729-3

Ultrasound modulates the activity of different types of neurons in the visual cortex

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Abstract: Numerous studies have demonstrated the great potential of ultrasound neuromodulation (USN) in treating brain diseases. Since these diseases involve functional abnormalities in specific types of neurons across different brain regions, it is crucial for ultrasound to selectively target and modulate the dysfunctional neurons. In this study, a USN system compatible with two-photon imaging (2PI) was employed to investigate the effects of USN on excitatory and inhibitory neurons in the visual cortex of mice at the cellular level. Genetically encoded calcium sensors (GCaMP6s) were selectively expressed in excitatory and inhibitory neurons by injecting different viruses into the visual cortex (ML: -2.0 mm, AP: -2.8 mm, DV: -0.8 mm) of C57BL/6J mice. A glass imaging cranial window was placed above the cortex, enabling 2PI during USN. Ultrasound with varying pressures (60, 160, 290, 400 kPa) and pulse repetition frequencies (PRF) (f=1 MHz, dc=50%, SD=0.5 s, P≈350 kPa, PRF=10, 1000, and 2000 Hz) was applied to the visual cortex. Then all mice were deafened surgically and subjected to both light stimulation of the eye and the aforementioned ultrasound stimulation after a 5-day recovery period. The results showed that ultrasonic stimulation with different parameters excited inhibitory neurons and inhibited excitatory neurons in the visual cortex, regardless of the mice's hearing status. However, the regulatory effect was significantly reduced in the absence of hearing. Additionally, light stimulation of the eye alone excited inhibitory neurons and inhibited excitatory neurons in the visual cortex. Combining USN with light stimulation prolonged the excitation of inhibitory neurons and the inhibition of excitatory neurons. Next, we will further study the specificity and mechanisms of the response of excitatory and inhibitory neurons in different brain regions to ultrasound stimulation.

[NO-8] PIBM2024-0809-2

Sparse Scanning Structured Illumination Microscop Visualize Thick Samples in 3D

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Abstract: Optical three-dimensional (3D) microscopic imaging thick samples is of great importance in many fields, especially in biology. In this talk, sparse scanning structured illumination microscopy (SS-SIM) will be presented, which provides super-resolution, optically sectioned images for thick samples. In SS-SIM, structured patterns of different orientations and different phase shifts are generated by resonantly scanning a focused light and modulating its intensity sinusoidally. Three-dimensional optical sectioning is realized by phase-shifting operation of the structured illumination. Furthermore, a pixel-reassignment-based algorithm (PR-SIM) is proposed for super-resolution reconstruction of SS-SIM. Compared to frequency domain based algorithms (FDAs), PR-SIM is much faster and more immune to fringe distortion in that it processes the raw images locally, in the spatial domain. The reconstruction speed of PR-SIM can be enhanced by skipping empty regions in the image, and further enhanced by employing GPU-base parallel calculation. Eventually, super-resolution and optical-sectioned fluorescence imaging with a penetration depth of ~200 micrometers has be performed, implying a great potential for deep tissue imaging.

[NO-9] PIBM2024-0804-2

Multi-module recording of neuronal activity and structures using graphene microelectrode arrays in the study of Niemann -Pick disease

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Abstract: Simultaneously recording network activity and ultrastructural changes of the synapse can significantly advance our understanding of the structural basis of neuronal functions. The intricate changes in neuronal activity at millisecond-scale and the minute structural modifications at the synapse that are smaller than the diffraction limit present considerable hurdles for this undertaking. Here, we introduce a multi-module recording system based on graphene microelectrode arrays (G-MEAs), which facilitate high-resolution imaging at different scales and permit electrophysiological recordings with high temporal precision. In conjunction with G-MEAs, we also apply a straightforward machine learning algorithm to streamline the analysis of extensive data gathered from microelectrode array recordings. We illustrate that the integration of G-MEAs, machine learning-based spike analysis, and four-dimensional structured illumination microscopy (4D-SIM) provides a powerful tool for observing the effects of disease progression on hippocampal neurons. Furthermore, treating neurons with an inhibitor of intracellular cholesterol transport to mimic Niemann-Pick disease type C (NPC) results in a significant enlargement of synaptic boutons compared to untreated neurons, ultimately impairing neuronal signaling capabilities.

[NO-10] PIBM2024-0730-18

Versatile photoacoustic fiberscopy for comprehensive assessment of sepsis-induced brain oxygenation dysfunction

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Abstract: Sepsis, a leading cause of death worldwide, induces systemic inflammation and organ damage, potentially leading to fatal outcomes. Despite significant interest in sepsis-induced brain injury, the underlying mechanisms remain incompletely understood. This study introduces a novel, compact, and flexible photoacoustic fiberscope for high-resolution, real-time imaging of brain oxygenation dysfunction in sepsis models. Our fiberscope utilizes dual-optical-fiber structure, for the guidance of laser pulses and detection of laser-induced ultrasound waves, respectively. This design of imaging probe offers three versatile operational modes:

a. "Plug-on" mode: Enables longitudinal monitoring of oxygenation impairment in freely moving animals.

b. Dynamic mode: Captures weakened cerebrovascular responses in septic conditions with enhanced temporal resolution.

c. Cortex-wide mode: Provides a comprehensive evaluation of brain dysfunction, particularly visualizing heterogeneity in brain dysfunctionality under septic conditions.

The "plug-on" and dynamic modes achieve a 0.2 Hz frame rate with a 1.2 mm × 1.2 mm imaging area, while the cortex-wide imaging mode covers a 7 mm × 6 mm area in 2 minutes. The system maintains a lateral resolution of 5 μm across all modes.

This versatile imaging platform allows for comprehensive examination of oxygenation impairments, disruptions in oxygen extraction fraction (OEF) variations, and cortical hypoxia heterogeneity, providing a thorough assessment of brain dysfunction in septic conditions. The photoacoustic fiberscope's lightweight and versatile design facilitates extensive structural and functional assessments, paving the way for potential handheld or wearable applications in intensive care medicine.

The versatile fiberscopy offers a new imaging modality for precise assessment of sepsis-induced brain dysfunction, delivering critical insights for early detection, diagnosis, and intervention in sepsis management. This technology has the potential to revolutionize our understanding of sepsis-related brain injuries and improve patient outcomes in critical care settings.

[NO-11] PIBM2024-0824-1

Hyperscanning real-world interactions via functional near-infrared spectroscopy

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Abstract: With the aim of hyperscanning real-world interactions using functional near-infrared spectroscopy (fNIRS) technology, a distributed portable backpack system is implemented in the present study, enabling synchronous measurement of multi-subjects, wireless master-slave connections and lower power consumption. In order to achieve an integrated characteristic of miniaturization, movement freedom, high cost-effectiveness and hemodynamics profiling, the system is structured as a network of configurable optodes, equipped with maximum 24 dual-wavelength sources and 24 silicon photomultipliers. On-line digital lock-in detection based on multi-periodic reference-weighted counting algorithm is performed in each slave to separate the signals from the different source-detector combinations as well as the wavelengths. Phantom and hand movement paradigm experiments are designed to assess the fundamental performances of the implemented system, and validate the good raw signal quality with the static measurement fluctuation of < 1%, dynamic optical range of > 100dB, and temporal resolution of 20Hz, as 80 channels work simultaneously, as well as the feasible sensitivity for detecting task-evoked activation. The preliminary experiment suggests that, the proposed system has a capability of distilling the inter-brain activation patterns with acceptable temporal resolution, and bears high potential toward fNIRS-based social neuroimaging in real-world.

[NO-12] PIBM2024-0722-3

Research on Rare Earth-Doped Near-Infrared Probes in Neurodegenerative Disease Diagnosis and Mechanisms

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Abstract: Compared to traditional dyes, rare earth near-infrared probes exhibit superior stability and adjustable luminescence properties with penetration in deep tissues. This enables the realization of multi-modal imaging, quantitative analysis of cells, tissues, and living organisms, as well as research into disease mechanisms. In this study, by constructing upconversion nanoparticles (UCNP) doped with different rare earth elements and by regulating the structure and luminescent efficiency of UCNP, high sensitivity and rapid detection of target antigens and RNA were achieved through the fluorescence resonance energy transfer (FRET) effect and surface plasmon resonance (SPR) effect. In addition, we also achieved long-term stable monitoring of microorganelles, target proteins, energy, and ions in the neurodegenerative disease microenvironment. We finally elucidated the dynamic changes of cellular organelles and microenvironment during the onset of Parkinson's disease (PD), laying the foundation for exploring the pathogenesis of PD

[NO-13] PIBM2024-0731-32

Interpreting neuronal projection features with functional specialization

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Abstract: Understanding the axonal projection characteristics of neurons is required for dissecting neural circuits, which determine brain function. The axonal projection shows the route of information transmission, while the functional response represents the content of the information delivered. Traditionally, neural circuits have been described on "one projection determines one circuit". However, with the notion that a single neuron can project to multiple brain regions, the relationship between neuronal projection patterns and functions needs to be re-understood. Here, we investigate the association between visual function and cortical neuronal projection patterns using the mouse visual cortex as a model. Combined with AAV virus to mark the fine structure of neurons, fMOST or confocal imaging to show the intact neuronal morphology or projection, two-photon imaging to record neuronal firing, chemo-genetics to regulate neural activity, it was analyzed that the relationship between neuronal structure and functions, includes intracortical projection pattern and basic visual information, subcortical projection pattern and instinctive visual fear behavior. In layer L2/3 of the primary visual cortex, intra-telencephalic projection neurons show a projection preference for functional information such as color and motion vision versus higher visual cortical regions such as LI and AM. In layer L5, extra-telencephalic projection neurons exhibit a specific multi-regions projection pattern for instinctive visual fear behavior. It reveals the transmission and processing of functional information in the multi-regions projection of neurons. Further understanding of the transmission and processing of visual information also give a new insight to explore the structure and organization of neural circuits.

[NO-14] PIBM2024-0731-34

A stereotaxic template for integrating the neuroinformation of the mouse brain with isotropic one-micron resolution

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Abstract: A stereotaxic template of the mouse brain with spatial localization capability at the single-cell level is essential for locating and integrating multi-omics and single-neuron circuit information. Combining the MOST imaging technique and the improved sample preparing method for large volume tissue, we developed a 3D mouse brain template, based on a Nissl-stained cytoarchitecture image dataset with isotropic one-micron resolution. With this brain template, we built a web platform that facilitates the registration of miscellaneous neuroinformation, including the 3D whole brain image, the 2D brain slices, as well as the reconstructed neuron morphology data. With the benefit of this template, we could achieve the co-localization of neural data with different sources, obtain a global view of the whole brain scale, and integrate the knowledge from different research fields of neuroscience.

Translational Biophotonics

[TO-1] PIBM2024-0731-16

SERS-AI strategy for accurate classification and rapid diagnosis of various meningitis

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Abstract: Cerebrospinal fluid (CSF)-based pathogen or biochemical testing is the standard approach for the clinical diagnosis of various types of meningitis. However, misdiagnosis and missed diagnosis often occur due to unusual clinical manifestations and the time-consuming nature of the process, as well as its low sensitivity and poor specificity. As a molecular vibration spectroscopy with high sensitivity and rapid detection characteristics, Surface-Enhanced Raman Spectroscopy (SERS) has been applied in various fields and has the potential to provide a rapid and highly sensitive diagnostic strategy for meningitis. Here, we propose a simple and reliable label-free CSF-induced SERS detection strategy and establish a machine learning (ML) model based on spectral information fused with baseline features, enabling rapid diagnosis and classification of meningitis. Stable and reproducible SERS spectra are obtained within 30 seconds by simply mixing colloidal silver nanoparticles (Ag NPs) with a CSF sample, achieving a relative standard deviation of signal intensity as low as 2.1%. Finally, an ML-assisted meningitis classification model is established based on the spectral feature fusion of characteristic peaks and baselines. Utilizing an optimized KNN algorithm, our model achieves a classification accuracy of 99% for autoimmune encephalitis, novel cryptococcal meningitis, viral meningitis, and tuberculous meningitis, while the baseline-corrected spectral data achieve an accuracy of 68.74%. The CSF-induced SERS detection method has the potential to provide a novel liquid biopsy approach for the diagnosis and early detection of various cerebral ailments.

[TO-2] PIBM2024-0819-18

Raman spectroscopy and microscopy for clinical applications

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Abstract: Raman techniques such as spectroscopy and imaging are widely utilized methods in clinical research. On the one hand, in order to follow up the haemodynamic change of dilated cardiomyopathy patient under immunoadsorption therapy in one year time span noninvasively and specifically, Raman spectroscopy combined with machine learning was used to study the clinical blood. The results showed that, not only a diagnostic accuracy of up to 96% was achieved, but also the clearance and reconstitution of IgG during the course of immunoadsorption treatment was tracked successfully and quantitatively, which indicated a highly consistent IgG quantification results with the commonly used immunoturbidimetry in clinical practice. These results show the combination of vibrational spectroscopic and chemometric methods holds the potential to follow hemodynamic changes after immunoadsorption therapy in dilated cardiomyopathy patients.
On the other hand, to investigate the potential of Raman microscopy in the digital pathological diagnosis of breast cancer, stimulated Raman scattering (SRS) images from 61 breast cancer clinical biopsies were analyzed with multi-instance learning algorithm in deep learning, reaching a diagnosis accuracy of 95%. Besides, the label-free SRS pathology images were visualized with the help of gradient-weighted class activation and semantic segmentation, which showed the benign and malignant regions on the tissues in a simple and clear way. The combination of SRS and deep learning algorithms show high potential to realize the label-free rapid digital pathological diagnosis of breast core needle aspiration biopsy.

[TO-3] PIBM2024-0819-19

Raman Spectroscopy and Machine Learning-Based Classification for Biochemical Characterization of Human Myopic Corneal Stroma and Animal Corneal Stroma

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Abstract: **Purpose**: To investigate the Raman spectrum and differential analysis of human and animal model corneal stroma in ex vivo using a confocal Raman micro-spectrometer built in the laboratory.
Methods: Seven fresh porcine corneas, six fresh rabbit corneas and thirty-eight human subjects were used for the study. Human corneal stromal lenticules are obtained from patients who have undergone small incision lenticule extraction (SMILE) surgery. A Raman microspectroscopy has been used to study the corneal structure of different species and its complete Raman spectrum have been obtained within the range of 700–4000 cm^{-1}. This study used Partial Least Squares Regression (PLS) for dimensionality reduction of Raman spectral data, followed by Support Vector Machine (SVM) to train the classification model.
Results: Ten characteristic peaks of human corneal stroma were found, with the stronger peaks appearing at 937 cm^{-1}, corresponding to proline, valine, and type I collagen; 1243 cm^{-1}, corresponding to Amide III of collagen protein; 1448 cm^{-1}, corresponding to the collagen protein and phospholipids; 1663 cm^{-1}, corresponding to the DNA and protein; 2940 cm^{-1} corresponding to the lipids and protein, which was the strongest Raman peak; and 3330 cm^{-1}, corresponding to the water. Eleven characteristic peaks were found in the Raman spectra of porcine and rabbit corneas. The Partial Least Squares Regression (PLS) components with relatively high contributions to the first 4 variances in the original spectral data are mainly concentrated in the wavelength range of 1099 cm^{-1} and 3300-3422 cm^{-1}. AUC value of human and animal corneal classification model based on PLS-SVM reaches 0.99. The Raman spectral curves of the three species were similar, but there were clear differences in the intensity of characteristic peaks.

Conclusions: The difference in Raman spectroscopic analysis of biochemical components between human myopia corneal stroma and animal corneal stroma mainly occurs in the spectral regions associated with nucleic acids and water molecules. Compared with rabbit cornea, the Raman spectra of human and porcine corneal stroma have higher similarity, indicating that porcine cornea may be a more accessible and valuable human corneal analogue. Raman spectroscopy can directly comparison among species, which may help establish the basis for the distribution of biochemical components in animal models or understand diseased corneas.

[TO-4] PIBM2024-0820-14

BEST IN PHYSICS of AAPM: First Demonstration of Quad-Modal PET/SPECT/Spectral-CT/CBCT On-Board Imaging for Guiding Radiation Treatment in Small Animals Using a Monte Carlo Model

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Abstract: We investigated a highly integrated quad-modal on-board imaging configuration combining positron emission tomography (PET), single-photon emission computed tomography (SPECT), spectral CT, and cone-beam computed tomography (CBCT) within a small animal radiation therapy (SART) platform, using a Monte Carlo model as a proof-of-concept. Triple on-board SPECT, spectral-CT, and CBCT imaging were achieved using a single photon-counting cadmium zinc telluride flat-panel detector. A partial-ring on-board PET imaging subsystem, coplanar with the triple imaging subsystem, was designed using a thallium bromide semiconductor detector. We evaluated the spatial resolutions of the PET, SPECT, and CBCT subsystems using simulated phantoms. The performance of the proposed quad-modal imaging system was validated through imaging a simulated phantom with multiple probes, including an iodine contrast agent and radioisotopes ^{18}F and ^{99m}Tc. The spatial resolution of CBCT imaging was estimated at 4.5 lp/mm at 10% MTF, equivalent to 111 µm, while the SPECT subsystem achieved a spatial resolution of no more than 1.2 mm. For the PET subsystem, the absolute peak sensitivity at the platform center was 18.5%, with an energy window of 175–560 keV, and the scatter fraction was measured at 3.5% using the NEMA NU-4 mouse phantom with a default energy window of 480–540 keV. The PET subsystem's spatial resolution exceeded 1.2 mm. All imaging probes were clearly identified within the phantom. The PET and SPECT images correlated well with the actual spatial distributions of tracers within the phantom. High-quality PET, SPECT, spectral-CT (including iodine contrast agent fraction and virtual noncontrast electron density images), and CBCT images demonstrated the system's comprehensive multi-modal imaging capabilities. These results demonstrate the feasibility of the proposed quad-modal imaging configuration within a SART platform, offering comprehensive image guidance at anatomical, functional, and molecular levels for radiation treatment beam delivery.

[TO-5] PIBM2024-0728-9

Multitask learning-powered large-volume, rapid photoacoustic microscopy with Airy beam

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Abstract: Large-volume photoacoustic microscopy (PAM) or rapid PAM has attracted increasing attention in biomedical applications due to its ability to provide detailed structural and functional information on tumor pathophysiology and the neuroimmune microenvironment. Non-diffracting beams, such as Airy beams, offer extended depth-of-field (DOF), while sparse image reconstruction using deep learning enables image recovery for fast imaging. However, Airy beams often introduce side-lobe artifacts, and achieving both extended DOF and rapid imaging remains a challenge, hindering PAM's adoption as a routine large-volume and repeatable monitoring tool. To address these challenges, we developed multitask learning-powered large-volume, rapid photoacoustic microscopy with Airy beams (ML-LR-PAM). This approach integrates advanced software and hardware solutions designed to mitigate side-lobe artifacts and achieve super-resolution reconstruction. Despite the potential of non-diffracting beams and sparse image reconstruction, previous efforts have often overlooked the simultaneous optimization of these aspects, leading to compromised imaging quality and limited applicability in clinical settings. Our work bridges this gap by focusing on comprehensive multitask learning, ensuring that ML-LR-PAM delivers artifact-minimized images with large-volume, high-resolution capabilities, thus enabling rapid and repeatable monitoring performance. We anticipate that the integration of these software and hardware advancements will facilitate ML-LR-PAM as a routine tool in both biomedical research laboratories and clinical applications.

[TO-6] PIBM2024-0730-4

In-vivo optical-resolution photoacoustic endoscopy on rat rectal tumor

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Abstract: Accurate detection of angiogenesis, a key characteristic in tumor development, is crucial for clinical diagnosis and treatment. Optical resolution photoacoustic endoscopy (OR-PAE) has proven to be a powerful tool for imaging the vasculature of the gastrointestinal (GI) tract. Several catheter designs have been reported, demonstrating high-resolution imaging and excellent adaptability. However, this technology has not yet been validated through in vivo studies in the GI tract. In this study, we developed a novel OR-PAE catheter and

performed imaging on an animal model of colorectal tumors. We successfully acquired in vivo photoacoustic and ultrasound images of rat rectal tumors. Hematoxylin and eosin (H&E) staining was conducted on pathologic sections of the rat rectum, and the results were consistent with the imaging findings. These promising results demonstrate that the optical-resolution photoacoustic endoscopic catheter has significant potential for visualizing the morphology of tumor angiogenesis in the gastrointestinal tract.

[TO-7] PIBM2024-0731-24

Exploring the mechanisms of Texaphyrin-Pt conjugate in overcoming tumor resistance assisted by photoacoustic spectral imaging

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Abstract: In this investigation, we explore the therapeutic efficacy of the Texaphyrin-Pt conjugate in tumor therapy, utilizing advanced photoacoustic imaging to dynamically monitor its metabolic characteristics in vivo. Our findings demonstrate the conjugate's potent capacity to suppress tumor growth. Nevertheless, the precise molecular mechanisms underpinning its ability to counteract resistance to platinum-based chemotherapy agents are not yet fully elucidated. Emerging evidence suggests that a metabolic shift from glycolysis to fatty acid metabolism could underlie the development of drug-resistance in tumor cells. Employing our newly developed 3D lipid photoacoustic spectral imaging system, we achieved rapid, three-dimensional visualization of tumor lipid profiles, which shed light on the lipid dynamics within drug-resistant tumors. Moreover, using photoacoustic microscopy, we quantified alterations in the size and quantity of lipid droplets, establishing a direct link between these morphological changes and resistance pathways. Further investigations into the mechanism of action of the Texaphyrin-Pt conjugate revealed that upon its release, Texaphyrin specifically and strongly binds to the C-myc oncogene — a gene frequently overexpressed in various tumors. This binding interaction, possibly synergizing with the known effects on the p53 tumor suppressor gene, serves to significantly inhibit cellular proliferation. Moreover, this interaction is theorized to circumvent the resistance typically observed with clinical platinum-based anti-cancer treatments by inducing profound metabolic transformations within the tumor cells. Our study elucidates novel molecular and metabolic strategies by which the Texaphyrin-Pt conjugate mitigates tumor resistance, highlighting the versatility of photoacoustic imaging in addressing complex biomedical questions and opens new paths for the design of future anticancer therapies.

[TO-8] PIBM2024-0730-3

Targeted Cyclo[8]pyrrole-based NIR-II Photoacoustic Tomography Probe for Suppression of Orthotopic Pancreatic Tumor Growth and Intra-abdominal Metastases

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Abstract: Pancreatic cancer is highly lethal. New diagnostic and treatment modalities are desperately needed. We report here that an expanded porphyrin, cyclo[8]pyrrole (CP), with a high extinction coefficient (89.16 L/g•cm) within the second near-infrared window (NIR-II) may be formulated with an αvβ3 specific targeting peptide, cyclic-Arg-Gly-Asp (cRGD), to form cRGD-CP nanoparticles (cRGD-CPNPs) with promising NIR-II photothermal (PT) therapeutic and photoacoustic (PA) imaging properties. Studies with a ring-array PA tomography system, coupled with analysis of control nanoparticles lacking a targeting element (CPNPs), revealed that cRGD conjugation promoted the delivery of the NPs through abnormal vessels around the tumor to the solid tumor core. This proved true in both subcutaneous and orthotopic pancreatic tumor mice models, as confirmed by immunofluorescent studies. In combination with NIR-II laser photoirradiation, the cRGD-CPNPs provided near-baseline tumor growth inhibition through PTT both in vitro and in vivo. Notably, the combination of the present cRGD-CPNPs and photoirradiation was found to inhibit intra-abdominal metastases in an orthotopic pancreatic tumor mouse model. The cRGD-CPNPs also displayed good biosafety profiles as inferred from PA tomography, blood analyses, and H&E staining. They thus appear promising for use in combined PA imaging and PT therapeutic treatment of pancreatic cancer.

[TO-9] PIBM2024-0827-1

Fast photoacoustic microscopy with unsupervised deep learning enabled real time image registration

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Abstract: In the imaging process of a fast-scanning OR-PAM system, correcting and matching distorted images is critical for accurately characterizing biological tissue structures and enabling quantitative analysis. Traditional registration algorithms are often time-consuming and less effective, which limits their practical application. In this study, we present an unsupervised learning-based registration network specifically designed to address distortions in photoacoustic images, aiming to enhance both the accuracy and real-time performance of photoacoustic imaging. Our method does not require ground truth input, which is a significant advantage over other learning-based methods. It utilizes mean squared error and mutual information as similarity measures to approximate distorted images to their undistorted counterparts. We first apply this algorithm to correct artifacts within images of the mouse ear vasculature. Subsequently, we extend the method

to address distortions between adjacent B-scan image sequences. The results demonstrate that our approach effectively corrects distortions both within individual images and between image sequences. Compared to traditional intensity-based registration algorithms, our method achieves a throughput improvement by several times, significantly enhancing processing speed. This advancement confirms that the proposed method can accurately and in real-time restore and register fast-scanning photoacoustic microscopy images. It provides a powerful tool for extracting dynamic vascular structure and functional information, thereby advancing the capabilities of high-speed OR-PAM imaging techniques.

[TO-10] PIBM2024-0801-4

Advanced imaging technologies and applications based on photoacoustic remote sensing

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Abstract: In recent years, photoacoustic microscopy (PAM) technology has attracted widespread attention in fields such as biomedicine and materials science due to its high-resolution and high-sensitivity characteristics. As an emerging non-invasive imaging method, photoacoustic remote sensing (PARS) further extends the application scope and potential of photoacoustic microscopy. Different from conventional PAM, PARS is based on the elasto-optic effect, utilizing a continuous probing beam to detect photoacoustic signals. When pulsed laser light is absorbed by the target sample, the local pressure increases, causing changes in the sample's refractive index, which ultimately alters the reflectivity of the probing beam. This report presents our latest research advancements in PARS technology, particularly focusing on innovations in multi-wavelength, high-resolution imaging and polarization imaging. We have developed a multi-wavelength PARS microscopy that efficiently acquires the optical absorption properties of samples, enabling high-resolution imaging of different tissues or materials. Additionally, by incorporating polarization-sensitive technology, we have successfully achieved high-contrast imaging of anisotropic materials, revealing the anisotropic distribution within biological tissues. Moreover, the incorporation of GPU acceleration and deep learning algorithms has also significantly enhanced the imaging speed of PARS. We have also conducted extensive explorations into the applications of PARS. In the field of biomedical imaging, multi-wavelength PARS provides precise spatial distribution information of biological tissues, which aids in the early diagnosis of tumors. In non-destructive testing, the high spatial resolution and non-contact nature of PARS technology make it highly effective for detecting material defects and other related applications. In summary, we have achieved significant advancements in PARS, including improvements in spatial resolution, spectral imaging capabilities, polarization imaging, and imaging speed. These highlight the considerable potential of PARS in both biomedical and material imaging.

[TO-11] PIBM2024-0731-54

Combined ultrasound/photoacoustic imaging for *in vivo* evaluation of microbubble-mediated ultrasonic cavitation therapy

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Abstract: Clinical studies have demonstrated that ultrasound-targeted microbubble destruction (UTMD) therapy enhances tumor treatment outcomes. UTMD improves vascular permeability and enhances blood perfusion through the cavitation effect produced by microbubbles under ultrasound. The state of blood oxygen function and vascular structure of tumor tissue is closely related to therapeutic efficacy. Existing studies primarily utilize ultrasound contrast imaging to evaluate the effects of UTMD on tumor blood perfusion; however, there are relatively few *in vivo* studies focused on the impact of UTMD on tumor blood oxygen functionality and vascular structure. In this study, a multimodal efficacy assessment scheme is proposed: Ultrasound combined with photoacoustic imaging was used to investigate the changes in hemoglobin distribution, blood oxygen, and blood perfusion in tumor tissue before and after UTMD. Phosphorescent *in vivo* oxygen sensing was employed to assess the impact of UTMD on tumor oxygen partial pressure. The results of model animal experiments showed that after UTMD treatment, the hemoglobin signal in tumor vasculature was enhanced, the oxygen saturation (SaO_2) increased by about 15.5%, and the microvascular structure in the deep tissue became clearer. Furthermore, the filling area of microbubbles in the tumor increased, the perfusion index (WipI) increased by about 371.75, the peak intensity (PE) increased by about 591.04, and the partial pressure of oxygen in the tumor increased by about 45.3%. This study provides more comprehensive evaluation information for clinically promoting ultrasound microbubble cavitation therapy.

[TO-12] PIBM2024-0729-4

Innovative Approaches for Structural and Functional 3D Imaging of PACT

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Abstract: Photoacoustic computed tomography (PACT) is a powerful biomedical imaging modality, but faces challenges in both structural and functional imaging. Structurally, PACT suffers from suboptimal spatial resolution, hindering its 3D imaging capabilities. Functionally, wavelength-dependent optical attenuation poses challenges for deep functional imaging beyond the optical diffusion limit. In this work, we report novel approaches that significantly advance the performance of PACT for both structural and functional imaging. For structural imaging, we introduce novel 3D reconstruction methods that incorporate synthetic aperture focusing techniques and higher-order derivative back-projection algorithms. These innovations enable virtual point

reconstruction and spatial frequency up-conversion, resulting in marked improvements to elevational and lateral resolutions. Yet, the spatial resolution remained limited by acoustic diffraction. To address this, we developed a novel 3D deconvolution scheme that effectively tackles the depth-dependent and spatially-varying point spread function. This strategy successfully breaks the acoustic diffraction limit, yielding enhanced 3D visualization of complex biological structures. Rigorous validation through phantom and in vivo experiments confirms the superior image quality provided by our methods. For functional imaging, we develop a full-view optical 3D quantitative compensation model and a non-negative matrix factorization-based spectral unmixing scheme. This framework allows simultaneous recovery of blood oxygenation (sO_2) distributions and extrinsic contrast agent signals, even in deep tissue regions with substantial optical fluence attenuation. The proposed techniques enable high-dynamic-range, high-resolution, and deep-tissue 3D functional imaging, overcoming critical limitations in conventional PACT approaches. Collectively, our work provides powerful new tools for advanced structural and functional biomedical imaging using photoacoustic tomography.

[TO-13] PIBM2024-0731-57

Learning-based imaging methods for high quality photoacoustic tomography

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Abstract: Photoacoustic tomography (PAT) has been an active research topic among recent years because of its promising advances in clinical and pre-clinical biomedical imaging. The image formation of PAT involves computational image reconstruction and image processing, and therefore requires specialized computer algorithms for high quality imaging. To address this problem, our group has carried out extensive research on advanced imaging algorithm for PAT in recent years. Specifically, thanks to the recent development in deep learning technology, we have adopted a number of learning-based methods for PAT imaging. These methods includes self-supervised learning-based image restoration, physics-informed learning-based image acquisition, and quantitative PAT imaging accelerated with deep learning and etc. Based on a commercial multispectral PAT imaging system, we have tested these methods with extensive imaging experiments on simulation targets, imaging phantoms, and in vivo small animal imaging sessions. The results demonstrate the potential of learning-based methods for the enhancement of image resolution and imaging quality for PAT.

[TO-14] PIBM2024-0731-20

Label-free structural and functional cellular imaging of fresh ophthalmic tissues with dual-mode full-field optical coherence tomography

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Abstract: The structural and functional imaging of ophthalmic tissues in cellular level plays an important role

in the understanding and evaluation of the physiology and pathology of ophthalmic diseases. In this study, we developed a dual-mode full-field optical coherence tomography (FFOCT) based on Linnik interferometry that is capable of acquiring high-resolution three-dimensional label-free cellular images of freshly excised ophthalmic tissues. While The FFOCT static mode offers the structural contrasts gained from refractive index gradients of the sample, the FFOCT dynamic mode gains color-coded functional contrast induced by endogenous cell motility without fluorescent dyes but the temporal analysis of interferometric signals. Our system achieved a lateral resolution of 0.5μm and an axial resolution of 1.7μm, with an imaging field of view of 320μm × 320μm at an acquisition speed of 100 Hz. Imaging experiments on both normal and pathological human or animal ophthalmic tissues have been performed using the dual-mode FFOCT system. We show that while the static FFOCT images better reveal the relative stationary cellular structures like nerve fibers, vascular walls and collagens, the dynamic FFOCT images show enhanced contrast of various transparent cells, such as corneal epithelial cells and retinal ganglion cells with active intracellular metabolic motions, offering complementary information of major corneal and retinal layers. With dual-mode FFOCT images, the structural and functional characteristics of human corneal grafts and pathological corneas as well as normal and glaucomatous mouse retina have been explored and quantified at cellular level without the need for contrast agent labelling, offering new image biomarkers for ophthalmic graft function evaluation and early pathology detection. Our study has demonstrated that the dual-mode FFOCT system is a straightforward promising technique for label-free cellular imaging exploration and pathological analysis of ophthalmic tissues.

[TO-15] PIBM2024-0720-1

Full-field polarization state tomography technique based on coherent synthesis of polarization state and orthogonal polarization state separation method

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Abstract: Comprehensive optical imaging of the intensity, phase, and birefringent information of the biological sample is important because important physical or pathological changes always accompany the changes in multiple optical parameters. Current studies lack such a metric that can present the comprehensive optical property of the sample in one figure. In this paper, a polarization state synthesis tomography (PoST) method, which is based on the principle of polarization state coherent synthesis and demodulation, is proposed to achieve full-field tomographic imaging of the comprehensive information (i.e., intensity, phase, and birefringence) of the biological sample. In this method, the synthesis of the polarization state is achieved by the time-domain full-field low coherence interferometer, where the polarization states of the sample beam and the reference beam are set to be orthogonal for the synthesis of the polarization state. The synthesis of the polarization state enables two functions of the PoST system: (1) Depth information of the sample can be encoded by the synthesized polarization state because only when the optical path length difference between the two arms is within the coherence length, a new polarization state can be synthesized; (2) Since the scattering coefficient, refractive index and the birefringent property of the sample can modulate the intensity and phase of the sample beam, the synthesized polarization state is sensitive to all these three parameters

and can provide the comprehensive optical information of the sample. In this work, the depth-resolved ability and the comprehensive optical imaging metric have been demonstrated by the standard samples and the onion cells, demonstrating the potential application value of this method for further investigation of the important physical or pathological process of the biological tissues.

[TO-16] PIBM2024-0730-32

Oxygen Concentration Effect for Hypoxic Photodynamic Therapy

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Abstract: Singlet oxygen ($^1O_2$), among the most reactive species, is extensively utilized in tumor therapy via photodynamic therapy (PDT). During PDT, $^1O_2$ is produced through a Dexter energy transfer mechanism, involving electron exchange between the triplet excited state of the photosensitizer and the triplet ground state of O_2. Conventional wisdom suggests that O_2 concentration dramatically impacts $^1O_2$ generation, thus playing a dominant role in PDT efficiency. Consequently, the therapeutic efficacy of PDT is believed to be significantly suppressed in hypoxic tumor environments. To address this, numerous strategies have been developed recently to enhance PDT efficiency in low O_2 conditions. However, our research challenges this conventional understanding. We have discovered that for certain photosensitizers, such as the widely studied chlorin e6 (Ce6), the generation of $^1O_2$ via photosensitization remains independent of O_2 concentration, extending from normoxic to hypoxic environments. This finding overturns the previously held belief that hypoxia severely limits PDT efficacy due to reduced O_2 availability. Our results indicate that the efficiency of $^1O_2$ generation by Ce6 is not significantly affected by varying O_2 levels, suggesting that PDT can remain effective even in hypoxic tumor regions. This revelation opens new avenues for PDT applications, potentially simplifying treatment protocols and broadening the scope of tumors that can be effectively targeted by PDT, regardless of their oxygenation status.

[TO-17] PIBM2024-0801-3

Design, synthesis, and application of BODIPYs phototheranostic agents

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Abstract: Phototheranostic is a new clinical cancer treatment method with the advantages of precise positioning and light controlled therapy, providing an effective means for the precise diagnosis and efficient treatment of diseases such as cancer. Developing high-performance phototheranostics agents is the key to promoting the clinical application of phototheranostic. BODIPY dyes, as a common near-infrared fluorescent dye, have advantages such as high molar extinction coefficient, high fluorescence quantum yield, good

photostability, easy structure modification, and less susceptibility to environmental solution pH. They have gradually become a research hotspot in recent years. We designed and synthesized several multifunctional BODIPY phototherapeutic agents by regulating the conjugated structure of BODIPY, introducing push/pull electron groups, covalent coupling/supramolecular assembly of chemotherapy drugs, and evaluated their phototherapeutic performance using cell and mouse tumor models.

[TO-18] PIBM2024-0731-38

Synthetic optical reporter probes for apoptosis imaging

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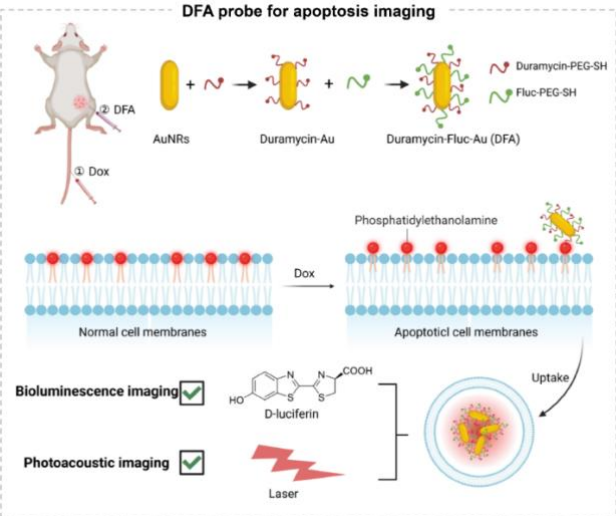
Abstract: Apoptosis is an important form of physiological death in multicellular organisms and is a programmed cell death regulated by specific mechanisms. Phosphatidylethanolamine (PE) translocation is considered a hallmark event of cellular apoptosis. The development of non-invasive multi-modality probes targeting PE for apoptosis detection holds great promise. Herein, we have developed a dual-modality imaging probe, Duramycin-Fluc-AuNRs (DFA), for detecting apoptosis in tumor cells. DFA is created by linking duramycin peptide and firefly luciferase (Fluc) recombinant protein to gold nanorods (AuNRs) via PEG. Duramycin exhibits high affinity for PE, while Fluc produces robust bioluminescence signal upon substrate binding, and AuNRs enhance imaging resolution and longitudinal capability through photoacoustic conversion. The prepared DFA probe demonstrates low toxicity in both cells and mice, showcasing its potential for in vivo applications. In A549 and 4T1 cell lines, the bioluminescence signal of the DFA probe increases with the degree of doxorubicin (Dox)-induced apoptosis. At the mouse level, mice with Dox-triggered apoptosis in tumor sites exhibit higher bioluminescence and photoacoustic imaging signals. Thus, this dual-modality bioluminescence/photoacoustic imaging platform holds significant potential for detecting cellular apoptosis and providing high-performance imaging information.



[TO-19] PIBM2024-0730-17

Proximity-induced Electrochemiluminescence sensor for capturing of exosomes and probing internal microRNAs related to cancer cell apoptosis

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Abstract: Exosomal microRNAs (miRNAs) play critical regulatory roles in many cellular processes, and so how to probe them has attracted increasing interest. Based on framework and spherical nucleic acids synergistically enhanced electrochemiluminescence (ECL) nanosensors, a dimeric truncated triangular pyramid (TTP) DNA nanoplatform was proposed. The constructed ECL sensing platform was connected to the other TTP nanostructure, which appended exosome aptamer at the top edges that can gather exosomes on the sensing platform and release miRNA in situ after exosome lysis. The proximity effect enables to rapidly capture miRNAs prior to diffusion, improving the detection sensitivity of exosomal miRNAs. The practicability of this design has been well verified in the detection of exosome miR-21 from MCF-7 and Hela. Furthermore, in order to examine the specific mechanism of miRNAs in the physiological activities of cancer cells, detection of miR-21 during early apoptosis of A549 and MCF-7 was carried out by the proposed sensing platform. The results demonstrated that the expression level of the anti-apoptotic miR-21 decreased during the early stage of apoptosis in both of the two cancer cells compared to normal ones, which means that the low level of miR-21 is related to the apoptosis of cells, rather than support the growth of cancer cells. In contrast, miR-21, which is highly expressed in normal cancer cells, promotes the pathway of cancer cells growth or suppresses the expression of genes related to apoptosis, that causes cells to exhibit a malignant phenotype. This phenomenon provided timely feedback for cancer treatment, which means the trend of cancer development, even the therapeutic effect can be precisely assessed by monitoring miRNAs associated to cancer such as miR-21.

[TO-20] PIBM2024-0731-47

Photo-Triggered Pt (IV)-Coordinated Nanoprodrug for Tumor Therapy

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Abstract: Rapid, efficient, and precise cancer therapy is highly desired. Here, this work reports solvothermally synthesized photoactivatable Pt(IV)-coordinated carbon dots (Pt-CDs) as a novel orange light-triggered anti-tumor therapeutic agent. The homogeneously distributed Pt(IV) in the Pt-CDs (Pt: 17.2 wt%) and their carbon cores with significant visible absorption exhibit excellent photocatalytic properties, which not only efficiently releases cytotoxic Pt(II) species but also promotes hydroxy radical generation from water under orange light. When triggered with a 589 nm and 695 nm laser, Pt-CDs possesses the ultrastrong cancer cell killing capacities of intracellular Pt(II) species release, hydroxyl radical generation, and acidification, which induce powerful immunogenic cell death. Activation of Pt-CDs by a single treatment with a 589 nm and 695 nm laser effectively eliminated the primary tumor and inhibited distant tumor growth and lung metastasis. This study thus presents

a new concept for building photoactivatable Pt(IV)-enriched nanodrug-based CDs for precision cancer therapy.

[TO-21] PIBM2024-0813-2

High-spatiotemporal resolution microwave-induced thermoacoustic imaging

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Abstract: How to obtain physiological and pathological information from deep biological tissues in real-time, with high resolution and non-invasively, for the early diagnosis and continuous monitoring of major diseases is a pressing challenge in the field of biomedicine. Microwave thermoacoustic imaging technology, which is based on the principle of effective conductivity differences, employs nanosecond pulsed microwaves as the excitation source to stimulate biological tissues, resulting in the generation of ultrasound. This ultrasound can provide insights into the structural and functional characteristics of biological tissues, facilitating non-destructive imaging of physiological and pathological conditions. Microwave-induced thermoacoustic imaging offers an effective combination of high spatiotemporal resolution, excellent contrast, and deep tissue imaging capabilities. It has already demonstrated significant results in several key areas, including brain structure imaging, breast tumor screening, imaging of human arthritis, and liver fat content detection, indicating a promising future for broader applications. As this technology continues to mature and improve, it is anticipated that microwave-induced thermoacoustic imaging will play an increasingly vital role in advancing biomedical research and development. This report will outline the research progress made by our team in recent years regarding high spatiotemporal resolution microwave thermoacoustic imaging technology for deep biological tissue detection, emphasizing the significance and potential application value of this technology in the field of biomedical imaging.

[TO-22] PIBM2024-0729-16

Volumetric Visualization of Whole-body Dynamics with Rapid Wide-field Photoacoustic Tomography (RAW-PAT)

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Abstract: Whole-body imaging is a crucial tool in advancing life sciences, offering a range of modalities for comprehensive analysis. Non-invasive volumetric visualization of intrinsic physiological processes and dynamics provides a macroscopic understanding of organ-level biological mechanisms. Photoacoustic imaging, which transcends the scattering limitations of pure optical imaging, uniquely captures spectral

absorption information in deep tissues. Despite its advantages, the full potential of photoacoustic imaging is constrained by challenges such as limited field of view, resolution, and overall imaging quality, particularly when assessing systemic dynamics. In this study, we introduce an advanced rapid wide-field photoacoustic tomography (RAW-PAT) system designed to overcome these limitations. RAW-PAT demonstrates extensive capabilities in structural, functional, and molecular 3D imaging, providing a comprehensive tool for analyzing complex biological systems. The system enables dynamic tracking and detailed analysis of multiple physiological parameters within a broad field of view, including the entire trunk and brain. Our results feature 3D dynamic imaging of the trunk with unprecedented quality, revealing intricate vascular networks and natural rhythmic organ motions. We also conducted whole-body pharmacokinetics studies, offering insights into systemic drug distribution patterns. The detailed 3D visualization of the brain, from the basicranial structures to the cortical regions, underscores RAW-PAT's potential for monitoring functional changes in response to pharmacological interventions and physical stimuli, with exceptional spatiotemporal resolution. Notably, the Circle of Willis, a critical cranial structure for cerebral blood supply, was meticulously visualized, highlighting RAW-PAT's deep-tissue imaging capabilities. Thus, RAW-PAT not only explores but fully leverages the advantages of photoacoustic imaging, positioning itself as an advancement in biomedical imaging and attracting substantial interest from the research community.

[TO-23] PIBM2024-0730-12

Fast Simulation of Three-dimensional Photoacoustic Imaging with Arbitrary Ultrasound Transducer Arrays

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Abstract: Three-dimensional (3D) photoacoustic (PA) imaging is a powerful technique for non-invasive visualization of biological structures and functions. Accurate simulation of 3D PA signal propagation and reception is crucial for system design, optimization, and image reconstruction algorithm development. However, existing PA simulation tools are typically grid-based (e.g., k-Wave), which can be computationally intensive, especially for large imaging volumes and complex transducer array geometries. The high computational burden of grid-based 3D photoacoustic simulations limits their practical applicability and scalability, particularly when exploring various transducer array configurations or performing extensive parametric studies. To address this problem, we present here a grid-free alternative based on Field II program to simulating 3D PA imaging with arbitrary ultrasound transducer arrays. The present approach makes uses of linear acoustic assumption, reciprocity principle, and analytical solution of spatial response of a rectangle receptor, eliminating the need for discretized spatial grids and thus greatly reducing the computational requirements. To demonstrate the utility of this approach, arrays of two different shapes were constructed and 3D point-spread-functions (PSF) were reconstructed to assess the quality of the corresponding PA images. In the first case is a ring array that can be translated along the z-axis to realize 3D scanning. The second case features two opposite matrix arrays that can be simultaneously rotated around the z-axis. Parametric study for each case was conducted to evaluate the influence of element size on the image quality. Results show that the elements should be sufficiently small to realize satisfactory 3D resolution. Since smaller elements have lower reception amplitude,

it indicates that in practice cautions should be paid to balance the trade-off between signal-to-noise ratio (SNR) and spatial resolution of 3D PA imaging. This work enables more efficient design and optimization of a 3D PA imaging system, and can thus be used to accelerate the research progress and its translation to practical applications.

[TO-24] PIBM2024-0729-15

Accurate Assessment of Endometrial Injury Based on Multiple Modalities of Endoscopic Optical/Acoustic Imaging

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Abstract: Endometrial injury (EI) is an important factor affecting infertility, and precise analysis of EI status and progression is crucial for guiding treatment and assessing prognosis. In clinical practice, key indicators such as endometrial morphology, elasticity and blood perfusion are often used to evaluate the degree of EI. However, current assessment methods are limited by sensitivity and resolution, such as ultrasound, which is performed outside the uterus. Hysteroscopy, the only endoscopic imaging method currently used within the uterus, has improved in resolution, but the visible depth has become shallower. These limitations make accurate evaluation challenging. Therefore, there is an urgent need to develop a new method that combines multiple modalities that can accurately assess EI in terms of morphology and function for clinical use. In this study, we leverage the advantages of endoscopic imaging combined with multiple optical/acoustic modalities to achieve a multimodal, accurate, and noninvasive assessment of EI in small animals in vivo. We use the high contrast and depth advantages of endoscopic photoacoustic imaging to evaluate endometrial microvascular perfusion. We employ the high resolution of endoscopic optical coherence tomography (OCT) imaging to visualize the microscopic details of the endometrium. Additionally, based on the derivate technology of the OCT, we use the endoscopic optical coherence elastography to detect the elasticity changes of the endometrium. By integrating various endoscopic imaging methods, ultimately allow us to continuously monitor the progression of EI from multiple dimensions of morphology and functional performance, as well as the time sequence of early changes and prognosis progression. This comprehensive monitoring provides imaging references for accurately assessing various degrees of EI, ultimately aiding in clinical treatment guidance and predicting recovery.

[TO-25] PIBM2024-0930-2

A frequency-domain index for quickly selecting optimal down-sampling factor in photoacoustic imaging

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Abstract: Photoacoustic microscopy (PAM) has emerged as a rapidly advancing non-invasive medical imaging method in recent years. However, slow imaging speed has impeded its widespread adoption in clinical applications. In certain scenarios, sparse spatial sampling is essential for PAM so there is a trade-off between spatial resolution and imaging speed. To address this limitation, we propose a frequency domain index based on cumulative power difference (CPD) to determine rapidly the optimal down-sampling factors. In this study, the structural images of mice ears were acquired by the PAM system. Subsequently, the optimal down-sampling factor was determined through CPD analysis of these images via interpolation. Finally, the correlation between cumulative power difference and the image quality loss curve were analyzed. The results indicate that the quality of the reconstructed images decreases with the increasing down-sampling factor. Moreover, the cumulative power difference is an effective tool for rapid assessment of reconstruction image quality degradation due to varying down-sampling factors.

[TO-26] PIBM2024-0703-1

Label-free, non-contact, high-resolution quantitative imaging of tissue chromophores using Spatial Frequency Domain Imaging (SFDI)

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Abstract: Tissue chromophores, such as oxy-hemoglobin, deoxy-hemoglobin, water, and lipids, are important biomarkers for various diseases and physiological processes. The quantification of those chromophores has been challenging due to the confounding effect of tissue absorption and scattering. Spatial Frequency Domain Imaging (SFDI) is an emerging label-free imaging technique that can provide quantitative chromophore concentrations in tissue. It has been applied to various biomedical scenarios for the mapping of chromophores, including burn wound monitoring, tumor monitoring, clinical tissue flap monitoring, inflammation monitoring, brown fat identification, blood lipids monitoring, and others. Using sinusoidal illumination patterns of specific spatial frequencies, SFDI can give quantitative optical absorption and reduced scattering maps at different wavelengths. The optical absorption at different wavelengths is used to calculate chromophore concentrations by solving a set of linear equations based on Beer's law. The key to accurate quantification of all four chromophores is accurate optical absorption measurement at sufficient number of wavelengths, which has been a major challenge. To address this issue, we develop a hyperspectral SFDI system that is able to measure tissue optical properties in the 680 – 1300 nm wavelength range. The light source is custom-built by a broadband lamp coupled with a monochromator. The DMD spatially modulates the light and generates sinusoidal illumination pattern which is then projected onto the tissue. The reflectance map is collected by the camera for subsequent processing. With the proposed system, we'll demonstrate quantitative mapping of water and lipid content in tissue using NIR-SWIR wavelengths. Last, in a proof-of-concept study, we show that oxy-hemoglobin, deoxy-hemoglobin, and oxygenation can be quantitatively imaged with a speed of 1000 Hz in a label-free, non-contact manner, which is two orders of magnitude faster than the state-of-the-art.

[TO-27] PIBM2024-0730-23

Label-free two-photon imaging: From near-infrared to visible excitation

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Abstract: Two-photon microscopy (TPM) has long been considered a powerful label-free imaging tool for biomedical research. However, specifically highlighting tissue structural components using label-free TPM imaging is still challenging to date, and thus seriously hindered the popularization and application of this technique. To this end, we induced a 520 nm excitation light into the TPM imaging system, as an excellent supplementary to the traditional near-infrared light excitation, to include short-wavelength endogenous fluorophores. Meanwhile, fluorescence spectral and fluorescence lifetime measurements were involved to allow clear discrimination of different endogenous fluorophores as well as functional imaging of biological tissues. These efforts would significantly improve the specificity of label-free TPM imaging. Utilizing the updated label-free TPM imaging systems, we (1) developed a novel method for *in vivo* and early detection of ischemic cerebral injury, based on quantitative cell metabolism characterization; (2) developed an automatic method for the identification of human coronary atherosclerotic plaque (CAP), based on 3D quantitative characterization of collagen and elastin fibers; (3) realized noninvasive imaging of microvascular network, *in vivo* monitoring of blood cell dynamics, and identification of arteries and veins based on the autofluorescence of hemoglobin, tryptophan, and elastin; (4) by integrating the aforementioned methods and studies, we performed systematic imaging on fresh human biopsy specimens with esophageal squamous cell carcinoma (ESCC) of different grades and derived a set of indicators for ESCC detection and grading. This study would promote the development of label-free detection technologies for biomedical research or applications.

[TO-28] PIBM2024-0731-8

Rapid and label-free histological imaging of unprocessed surgical tissues via Dark-field Reflectance Ultraviolet Microscopy

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Abstract: Intraoperative histopathology is essential for surgical margin assessment and is used to examine whether the tumor is completely excised. Routine pathological examination was performed by microscopic examination of tissues that were formalin-fixed and paraffin-embedded (FFPE), thinly sectioned, and stained. This is a lengthy and laborious process that fails to intraoperatively guide surgeons. Preparing frozen tissues is a more rapid alternative, but it still requires a turnaround time of ~30 min. Furthermore, freezing artifacts

caused by edematous and fatty tissues affect histopathological interpretation and diagnostic accuracy2. In addition, because of the destructive nature of FFPE histology and frozen sectioning, a large number of excised tissues may be wasted, compromising their value in downstream molecular and genetic analyses. Here, we present a rapid, nondestructive, and cost-effective histological imaging method called dark-field reflectance ultraviolet microscopy (DRUM). By using the endogenous mechanisms of both reflectance and absorption, DRUM enables label-free imaging of unprocessed and thick tissues with subcellular resolution and high signal-to-background ratio (SBR). To the best of our knowledge, DRUM can provide the image results for pathological assessment with the shortest turnaround time (2–3 min in total from sample preparation to tissue imaging). Furthermore, a virtual staining process was proposed to convert DRUM images into pseudo-colorized images (pseudo-colorized DRUM) and enhance the image familiarity of the pathologists. The capacity of DRUM was verified by imaging various tissues, including mouse brain and spleen tissues, human brain tumor tissues, and human breast cancer tissues. The results suggest that the proposed method can not only rapidly provide tissue architecture and subcellular features similar to conventional pathological images but also accurately differentiate between normal and tumor tissues.

[CRO-3] PIBM2024-0909-1

Transmission speckle contrast imaging combined with optical clearing

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Abstract: It is no secret that in addition to the metabolic nature of the disease, diabetes mellitus (DM) is considered a vascular disease due to its effect on the macro- and microcirculation of the vascular beds. Expansion of existing methods of diagnostics of the impact of DM on tissues and the vascular system are attractive at present. One of the promising non-invasive contactless methods of visualization of the vascular system is laser speckle-contrast imaging (LSCI). In the current work, the possibility of using magnetic resonance contrast agents (MR CAs) and X-ray CAs for LSCI and optical coherence tomography (OCT) of rat ears under conditions of developing alloxan-induced type 1 diabetes (T1DM) was studied for the first time. The aim of this study was to evaluate the effectiveness of using MR CAs such as Gadovist®, Magnevist®, X-ray CAs - Omnipaque®, Visipaque® as optical clearing agents (OCAs), as well as the nature of their effect on skin parameters and the vascular system under conditions of developing model T1DM. For the first time, the nature of the change in the contrast of the static part with a change in scattering was studied, which is an additional application for studying the efficiency of optical clearing and contributes to the multimodal application of the speckle imaging method.

Experiments of LSCI analysis was supported by the Russian Science Foundation grant No. 23-14-00287.

Poster Presetations

Analytical Biophotonics & Agri-Photonics

[AP-1] PIBM2024-0729-5

Rapid fluorescence microscopic image deconvolution through kernel learning

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Abstract: Fluorescence microscopic images are commonly degraded by intrinsic blurring, which hinders the observation of cellular components and capture of intra-cellular dynamics. Classic iterative Richardson-Lucy Deconvolution (RLD) algorithm can effectively improve the contrast and resolution of fluorescence microscopic images but is computationally expensive (usually requires dozens of iterations), particularly for three-dimensional (3D) data. Variants of RLD using manually designed unmatched backward projector have significantly accelerated deconvolution, however, they require careful parameter optimization to avoid introducing artifacts. We develop a new rapid fluorescence microscopic image deconvolution method, named Kernel Learning Deconvolution (KLD), which retains the original iteration procedure of RLD unchanged and automatically learns the forward/backward kernel in it from only one paired low-resolution and high-resolution images. The learned kernel reveals a similar pattern with handcrafted Wiener-Butterworth kernel and is robust to variants in the signal-to-noise ratio and the number of training samples. Compared to RLD and its variants, KLD eliminates the need for manual kernel modeling and parameter tuning, and achieves superior deconvolution performance with just two iterations. We demonstrate the enhanced deconvolution performance and speed of KLD across various cellular structures and imaging modalities, including two-dimensional wide-field microscopy, 3D confocal microscopy, and 3D lattice light-sheet microscopy. The low dependency on training data, superior deconvolution performance and speed of KLD are expected to accelerate biological discovery based on fluorescence microscopic images.

[AP-2] PIBM2024-0729-20

Transient stimulated Raman scattering spectroscopy and imaging

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Abstract: Coherent Raman scattering (CRS) can greatly enhance the cross-section of Raman scattering. It can provide information on the chemical bonds by selectively probing the intrinsic vibration modes of molecules.

Among the CRS techniques, Stimulated Raman Scattering (SRS) has been developed as an essential quantitative contrast for chemical imaging in recent years. However, the spectral resolution of the state-of-the-art SRS techniques is always lower than spontaneous Raman. This problem arises from the compromise between detection sensitivity and spectral resolution: as the nonlinear process benefits from pulsed excitations, the fundamental time-energy uncertainty limits the spectral resolution. Over the last decades, researchers in this field have looked forward to novel SRS techniques which combine high sensitivity with high temporal and spectral resolution.

Recently our team have reported on a novel technique named transient stimulated Raman scattering (TSRS), an alternative time-domain strategy that bypasses all these fundamental conjugations. We manipulated the quantum coherence of vibrational wave packets in the time domain by broadband femtosecond pulse laser; high-quality spectra near the natural-linewidth-limit were acquired at sub-mM sensitivity. Subsequently, we demonstrated the application of TSRS hyperspectral imaging by monitoring the metabolism of living Hela cells. We also preliminarily constructed a set of high-density Raman probes and further showcased its corresponding barcode imaging.

T-SRS prefers transform-limited ultrashort femtosecond laser pulses for excitation, suggesting higher compatibility with other nonlinear optical imaging modalities, such as multiphoton-excited fluorescence, second harmonic generation, ultrafast pump-probe techniques, etc. Combining T-SRS with those modalities shall open new opportunities for biomedical findings or even broader scenarios.

[AP-3] PIBM2024-0730-24

Stimulated Raman scattering microscopy enables histopathological grading of lung adenocarcinoma by artificial intelligence

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Abstract: The introduction of the International Association for Research on Cancer grading system has further interest in histopathological grading of lung adenocarcinoma risk stratification. The gold-stand histopathologic workflow uses hematoxylin and eosin (H&E) staining to reveal the cellular and tissue morphologies, yet it is time-consuming. Here, we demonstrated that stimulated Raman scattering (SRS) microscopy could reveal the largely heterogeneous histologic features of fresh lung tissues in a label-free and near real-time manner. A diagnostic network built based on images from about 70 patients could segment grading patterns of lung cancer with an accuracy of around 85%. This study demonstrates the potential of an AI–assisted SRS platform in evaluating the tumor grade of lung adenocarcinoma, which could help simplify the diagnostic workflow and provide timely and precise histopathology.

[AP-4] PIBM2024-0731-25

Optical Tweezers with AC Dielectric Levitation: A Powerful Approach to Microparticle Manipulation

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Abstract: Optical tweezers, with their high precision, dynamic control, and non-invasiveness, are increasingly important in scientific research and applications at the micro and nano scales. However, manipulation by optical tweezers is challenged by adsorption forces, including van der Waals forces, capillary forces, and electrostatic forces, which are present between micro- and nano-objects. Due to the inherent limitations of optical forces imposed by laser power, these adsorption forces are difficult to overcome. Inspired by maglev trains, we have developed a device that combines electric and magnetic fields to detach objects from hard substrates using alternating current (AC) dielectric levitation before manipulation with optical tweezers. We designed a transparent chip based on indium tin oxide (ITO) material that allows optical tweezers to operate objects within an AC electric field. We utilized micron-sized polystyrene (PS) microspheres as objects and elucidated the levitation mechanism through finite element simulation. Our experiments compared the maximum velocities (up to 15 μm/s) of four PS microspheres, each smaller than 20 μm, and yeast cells moved by optical tweezers, both before and after the application of AC power. According to Stokes' law, we calculated that the effective optical force was indirectly increased by up to four times. For larger particles, such as a 100 μm PS microparticle and a 200 μm micro-gear, AC dielectric levitation enabled manipulation by optical tweezers. Given its broad applicability and biocompatibility, AC dielectric levitation technology significantly expands the capabilities of optical tweezers, allowing for the manipulation of larger particles and cells. This advancement addresses the limitations of optical tweezers in handling large-scale particles and enhances their versatility in various applications.

[AP-5] PIBM2024-0731-37

Optical modeling and error correction for Measuring Inclined Surfaces with Confocal Microscopy

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Abstract: Confocal microscopy has wide applications in the biomedical field and is a highly precise and

efficient method for surface contour measurement. The Numerical Aperture (NA) of the confocal microscope limits the maximum surface slope that can be detected in the central field of view. However, the impact of the telecentricity of the confocal microscope objective on measurement errors in large field measurements has been rarely discussed. This paper introduces a general optical modeling method for confocal microscopy systems. Using this method, errors in confocal surface profilometry were investigated theoretically and experimentally. The results show that the telecentricity of the objective lens affects the vignetting coefficient when scanning inclined surfaces, and the peak intensity of the confocal signal is modulated by the vignetting coefficient at specific positions in the field of view. This explains the inaccurate positioning of slope structures at the edges of the field of view and provides suggestions for the design of large-field, high-precision confocal microscopes.

[AP-6] PIBM2024-0731-39

Self-interference digital optofluidic genotyping for integrated and automated label-free pathogen detection

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Abstract: Pathogen, prevalent in both natural and human environments, cause approximately 4.95 million deaths annually, ranking them among the top contributors to global mortality. Traditional pathogen detection methods, reliant on microscopy and cultivation, are slow, labor-intensive, and often produce subjective results. While nucleic acid amplification techniques such as polymerase chain reaction offer genetic accuracy, they necessitate costly laboratory equipment and skilled personnel. Consequently, isothermal amplification methods like recombinase polymerase amplification have attracted interests for their rapid and straightforward operations. However, these methods face challenges in specificity and automated sample processing. In this work, we develop a fully integrated label-free pathogen detection platform based on hyperspectral self-interferometry and digital microfluidics (DMF) , which solves the insufficient specificity and automation of traditional isothermal amplification-based pathogen detection. In contrast to conventional approaches, this study employs an innovative asymmetric direct solid-phase amplification technique to produce nanoscale specific amplicon monolayers on a self-interference substrate. Following this, hyperspectral interferometric detection is deployed to accurately measure optical thickness increments on the substrate. This novel strategy obviates the necessity for extended DNA hybridization processes and intricate exogenous labeling, thereby facilitating swift, label-free, and precise isothermal nucleic acid detection. Leveraging DMF technology, the developed sensor seamlessly integrates sample lysis, nucleic acid amplification, and detection processes. The research showcased herein achieves the detection of four indicators in a mere 50 minutes using a minimal sample volume of 4 μL. It successfully accomplishes specific Candida subtyping, with sensitivity reaching as low as 10^1 CFU·mL^{-1}. The method's efficacy is further underscored by its sensitive, specific, and integrated on-chip analyses of four Gram-negative bacteria, demonstrating exceptional detection performance and automated capabilities. This biosensor and platform offer a highly sensitive, specific, quantitatively accurate,

and automated alternative for pathogen detection, presenting versatile applications within the realm of disease diagnostic and precise medicine.

[AP-7] PIBM2024-0819-2

Single-shot probing of phase transients of laser-tissue interaction using cross-polarized common-path temporal interferometry

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Abstract: The transient information of tissues under femtosecond laser irradiation is crucial for understanding laser-tissue interactions, accurately interpreting measurement data, and gaining deeper insights into the physicochemical properties of the tissues. But the intensity probing based on scattering, reflection, and transmission primarily observes the morphological changes of the sample after the interaction with femtosecond laser pulses, making it difficult to dynamically monitor the evolution of early-stage low-concentration carriers and plasma. High-sensitivity phase probing will facilitate the recording of transient changes in early-stage carriers and plasma during the interaction between single or multiple femtosecond laser pulses and tissue. This approach can provide a basis for optimizing the parameters of femtosecond laser irradiation in tissues. Here, we use a cross-polarized common-path temporal interferometer to measure early-stage plasmas and laser-induced ultrafast refractive index transients with a temporal resolution of 500 fs. By using balanced detection with ultra-low noise, the phase sensitivity was enhanced to 3 mrad. For plasma diagnostics, this phase sensitivity is equivalent to a density-length product of 10^13 cm-2.

[AP-8] PIBM2024-0819-10

Measurement of multiscale viscoelastic properties for red blood cells with various optical tweezers

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Abstract: Technique of optical tweezers enables laser beam to exert controllable force on micron dielectric particles, with broad applications in fields such as biomedicine, biophysics, and nanotechnology. Single cell analysis techniques can reveal information on gene expression, metabolic activity, and signal transduction within cells, which are crucial for understanding cellular behavior and function. Due to their deformable size and difficulty in maintaining their activities, red blood cells present significant challenges for characterization and diagnostics, often making these processes complex and costly. In this study, we employed linear optical

tweezers to trap the red blood cells, manipulated cells by the modulated optical tweezers along with multi-frequency square waves, and investigated the viscoelastic properties of various red blood cells (e.g. thalassanemia). The optical system of linear optical tweezers enables precise and non-contact capture of cells, minimizing cell damage to a negligible level. By applying modulated excitations to the cells with multi-frequency squared waves and measuring the instantaneous responses of the cells with position detector, we were able to obtain the creep and recovery characteristics of the cells in various time domains. The cells, thus, could be successfully screened because of multiscale viscoelastic responses. Here a novel method for measuring the multiscale viscoelastic properties of cells by using linear optical tweezers and modulated optical tweezers was proposed, which might potentially provide a faster and more efficient tool to assess the mechanical properties of biological cells.

[AP-9] PIBM2024-0820-2

The investigation of the interaction mechanism between DOX and SIM with DNA using multispectral technology

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Abstract: Deoxyribonucleic acid (DNA), the fundamental basis of life, is a natural biological polymer and represents a prime target for numerous anti-cancer drugs. Doxorubicin (DOX), a typical cytotoxic agent employed in cancer treatment, primarily induces apoptosis in cancer cells by intercalating with DNA. However, the dose-dependent side effects of DOX, such as cardiotoxicity, hinder its dosage and efficacy. Reducing the side effects and enhancing the efficacy of DOX are the main problems to be solved. Simvastatin (SIM), a widely used statin in clinical practice, exhibits properties that augment the effectiveness of other anti-cancer drugs while reducing their side effects. Consequently, combination therapy involving DOX and SIM has garnered increasing attention. In this paper, the effect of SIM on the action of DOX and ctDNA was analyzed at the molecular level using surface-enhanced Raman spectroscopy (SERS) and UV-visible absorption spectroscopy techniques. It was found that when SIM and DOX were added to ctDNA in different sequences, the changes in Raman peak positions of ctDNA indicated that SIM would not interact with ctDNA, but would affect the effect of DOX on ctDNA, which was mainly shown to be synergistic, and UV-visible absorption spectroscopy further confirmed this conclusion. This study provides clinical guidance for the development of drugs to reduce the side effects of DOX and drug combination chemotherapy.

[AP-10] PIBM2024-0820-18

Rheological testing method of breast cancer cells by rotationally linear optical tweezers

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Abstract: As the fundamental unit of life structure and function, the cell has involved various scaling levels of research, such as cellular, subcellular, and even molecular levels. How to study cells while maintaining their physiological characteristics is the key to reveal the mysteries of life and to overcome diseases. With advantages of longer optical potential well of linear optical tweezers (LOT) and higher forward scattering radiation field of astigmatic beam, LOT has been proved to be an efficient way to manipulate bigger biological cells. In this paper, a rheological testing method in which breast cancer cell was stimulated by rotationally LOT for is proposed. Surface fluctuations reflecting cellular strain responses to rotationally LOT were detected dynamically and synchronously by scattered probe beam from local point of cell. Both amplitude and phase information of cell responses were analyzed to obtain rheological properties of cells. Cell manipulation of rotationally LOT with fast and dynamic detection can better achieve multi-frequency, high-precision, non-contact, and non-destructive measurement of cell mechanical characteristics, which might offer great importance for biomedical applications.

[AP-11] PIBM2024-0604-1

Research on water distribution detection of plant leaves based on microwave thermoacoustic imaging technology

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Abstract: The distribution of water content in plant leaves is an important index to measure plant physiology and biochemistry. At the same time，it is also an important basis for developing drought resistance strategies in the field of agricultural science. In this paper, the method on the detection of plant leaf water distribution based on Thermoacoustic imaging (TAI) is proposed that combines the advantages of microwave and ultrasound imaging, and a transmission-mode TAI system with excitation frequency of 3.0 GHz and a lateral resolution of 0.406 mm is constructed to realize the TAI imaging of Datura, Chrysanthemum and Perilla, respectively. In the meantime, through the quantitative analysis of TAI images before and after leaf water loss of three groups of Datura stramonium, it is verified that the change of plant leaf water can be characterized by the change of TAI image. The results indicated that the TAI technology proposed in this paper can be used to evaluate the water content and distribution of plant leaves, has the potential to achieve precision irrigation, and deepen the understanding of plant response to environmental changes in normal and stressed environments.

[AP-12] PIBM2024-0715-1

Scattered Light Field Separation and High-Quality Imaging Based on Low-Rank Sparse Matrix Decomposition

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Abstract: As light propagates through a scattering medium, interactions with the medium's particles cause scattering, producing scattered photons that disrupt the coherence and integrity of the light field. This scattering effect blurs the inherent characteristics of the light field, significantly impacting its efficacy in imaging and information transmission applications. To address this challenge, this paper proposes a technique based on low-rank sparse matrix decomposition (LSMD) aimed at quickly and accurately separating the scattered light field. This method leverages the sparse nature of the scattered light field and the low-rank characteristics of the background light field, validated through Monte Carlo simulations. By employing this technique in biological imaging, it effectively distinguishes clear imaging targets from background light, demonstrating its potential value in visualizing complex structures and detecting hidden objects. Compared to some classical denoising algorithms, such as Gaussian low-pass filtering, median filtering, wavelet transform, and total variation regularization, the proposed algorithm shows significant advantages in bright regions and achieves a higher proportion of scattered light removal. Experimental results indicate that this method excels in improving image quality and enhancing the signal-to-noise ratio, especially when dealing with complex biological samples and highly scattering environments. It provides higher contrast and clearer images. This innovative technology introduces new strategies for deep imaging and information extraction in scattering media.

[AP-13] PIBM2024-0724-1

Upconversion-based chiral nanoprobe for highly selective dual-mode sensing and bioimaging of hydrogen sulfide in vitro and in vivo

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Abstract: Chiral assemblies have become one of the most active research areas due to their versatility, playing an increasingly important role in bio-detection, imaging and therapy. In this work, chiral UCNPs/Cu_xOS@ZIF nanoprobes are prepared by encapsulating upconversion nanoparticles (UCNPs) and Cu_xOS nanoparticles (NPs) into zeolitic imidazolate framework-8 (ZIF-8). The novel excited-state energy distribution-modulated upconversion nanostructure ($NaYbF_4$@$NaYF_4$: Yb, Er) is selected as the fluorescence source and energy donor for highly efficient fluorescence resonance energy transfer (FRET). Cu_xOS NP is employed as chiral source and energy acceptor to quench upconversion luminescence (UCL) and provide circular dichroism (CD) signal. Utilizing the natural adsorption and sorting advantages of ZIF-8, the designed nanoprobe can isolate the influence of other common disruptors, thus achieve ultra-sensitive and highly selective UCL/CD dual-mode

quantification of H_2S in aqueous solution and in living cells. Notably, the nanoprobe is also capable of in vivo intra-tumoral H_2S tracking. Our work highlights the multifunctional properties of chiral nanocomposites in sensing and opens a new vision and idea for the preparation and application of chiral nanomaterials in biomedical and biological analysis.

[AP-14] PIBM2024-0727-2

Morphological characterization of oil gland in Citrus based on optical coherence tomography

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Abstract: This study focuses on the synergistic effect of the development of Citrus oil gland and the synthesis and accumulation of secondary metabolites can guide the cultivation of oil-free varieties, remove the bitter and numbing taste of fruit peels, promote the secretion of essential oils in citrus peels, exploring the potential market value of citrus fruits, enhancing the economic benefits of the citrus industry, and conducting relevant research. In this study, Optical Coherence Tomography (OCT) was used to perform non-destructive scanning of citrus peel and obtain high-resolution images of its internal oil glands. The precise segmentation of oil cell OCT images is performed using the U-Net model of Convolutional Neural Network (CNN) to extract the boundary and morphological features of oil glands. The segmented oil cell was also reconstructed in three dimensions, resulting in a cylindrical structure. The results show that the cross-sectional image of the oil cell was approximately an elliptical model, which could extract geometric parameters such as the long axis, short axis, and area of the oil cell. In addition, the morphological parameters and spatial distribution information of oil cells provides comprehensive, accurate, and efficient data support for the quality evaluation and grading of citrus, which helps optimize the quality control and scientific grading of citrus, enhance its market value and consumer recognition.

[AP-15] PIBM2024-0728-5

Advancing super-resolution imaging with all-optical three-dimensional addressable scanning multifocal structured illumination microscopy

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Abstract: Super-resolution fluorescence microscopy has witnessed rapid progress, emerging as an important tool for subcellular high-resolution imaging. Compared to other super-resolution imaging techniques,

structured illumination microscopy (SIM) possesses the advantages of excellent probe compatibility and low laser power demands, making it highly suitable for live cell imaging. However, SIM typically faces limitations in imaging depth, primarily caused by light scattering in biological tissues, restricting its application to thin samples. Multifocal structured illumination microscopy (MSIM) addresses this depth issue but sacrifices imaging speed. In three-dimensional (3D) imaging of thicker samples, conventional axial scanning involves layer by layer stage movement, which not only further slows down the imaging speed but also introduce mechanical inertia, leading to artifacts in reconstructed 3D super-resolution images. To overcome these challenges, we advanced our previously developed addressable scanning MSIM (AS-MSIM) technology using acousto-optic deflectors (AODs) to achieve all-optical 3D AS-MSIM imaging by introducing an electrically tunable lens (ETL). This breakthrough eliminates mechanical inertia, enabling rapid 3D super-resolution imaging of discrete regions of interest within the sample. Notably, this approach not only enhances 3D super-resolution imaging speed and flexibility but also reduces photobleaching and photodamage to the sample. We anticipate that this 3D AS-MSIM technique will broaden the practical applications of MSIM, revolutionizing super-resolution imaging across diverse research domains.

[AP-16] PIBM2024-0729-7

A Self-Calibrated High-Speed Delay Scanning System for Time-Domain Stimulated Raman Scattering Microscopy

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Abstract: To achieve natural linewidth-limited spectral lines in hyperspectral stimulated Raman scattering (SRS) imaging, we propose a self-calibrated high-speed delay scanning method using an all-plane-mirror system. This method, based on a Michelson interferometer design, eliminates dispersion and optical aberrations, ensuring minimal phase errors in T-SRS excitation and preserving the natural linewidth-limited spectral lines. The system incorporates a DFB laser with a linewidth of less than 3 MHz as a reference light source. By collecting interference fringe information of the reference light for spectral frequency calibration and interference fringes of the excitation light to calculate the excitation efficiency curve for self-calibration of the Raman spectrum. This method not only enables high-speed and high-precision delay scanning but also significantly enhances the spectral resolution and data reliability of SRS imaging.

[AP-17] PIBM2024-0729-8

Quantitative analysis of lipid unsaturation using spectral focusing coherent anti-Stokes Raman scattering microscopy

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Abstract: In Raman scattering spectra of oil or fat samples, the intensity ratio of specific Raman shifts exhibits strong correlations with the degree of lipid unsaturation. Consequently, coherent anti-Stokes Raman scattering (CARS) microscopy emerges as a valuable tool for analyzing the spatial distribution of lipid unsaturation within biological samples. Due to its high spectral resolution, spectral focusing CARS (SF-CARS) provides an ideal platform for investigating the distribution of lipid unsaturation. However, inherent non-resonant background (NRB) in CARS often introduces deviations in the measured CARS spectral peak positions. Additionally, the reduction in pulse overlap significantly decreases peak intensities at both ends of the spectral measurement range in spectral focusing methods. To eliminate these inaccuracies, we employ two simultaneous strategies: circularly polarized light modulation to suppresses NRB and correction of spectral intensity using non-resonant signals. This combined approach yields accurate CARS spectra. Building upon this foundation, we achieve precise analysis of lipid unsaturation by quantifying the intensity ratio of two specific bands in the C-H stretch region ($I_{=C-H}/I_{C-H}$). The established quantitative analysis technique based on CARS imaging holds promise for widespread applications in both chemistry and biological imaging.

[AP-18] PIBM2024-0729-11

Ferricyanide-mediated, electrocatalytic mechanism of electrochemical aptamer-based sensor supports ultra-sensitive analysis of cardiac troponin I in clinical sample

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Abstract: Rapid, reagent free and ultrasensitive analysis of cardiac troponin I (cTnI) is of significance for early diagnosis of acute myocardial infarction (AMI). The Electrochemical aptamer-based (EAB) sensors are promising candidates to fill this role, as they are reagentless and can be directly interrogated in complex matrices (e.g., blood). To achieve high sensitivity, EAB sensors typically require nanomaterials or other amplification strategies, which often involves cumbersome fabrication process. To circumvent this, here we develop a simple yet effective electrocatalytic electrochemical aptamer-based (Ec-EAB) sensor that utilizes target-induced regulation of catalytic mechanism to achieve ultrasensitive measurement of cTnI. In this assay, we employed a probe-attached redox reporter (i.e., methylene blue, MB) and a solution-diffusive redox reporter

(i.e., $Fe(CN)_6^{3-}$) to generate two signals, of which the latter is used to catalyze MB to amplify aptamer-mediated charge transfer. The recognition of target altered the diffusion of catalysts (2.2×10^{-9} mol/cm^2 in the target-free state versus 1.2×10^{-9} mol/cm^2 in the target-bound state) and thus electrocatalytical efficiency, enabling ultrasensitive measurement of cTnI with a 1000-fold improvement in their sensitivity (a limit of detection value: 10 pg/mL).

[AP-19] PIBM2024-0729-18

A fluorescence-based drug screening strategy for live-cell intracellular targets using cell-penetrating peptides delivery of non-permeable organic fluorescent probes

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Abstract: A drug screening strategy based on fluorescent probes is an important method for finding drugs that target cellular disease sites. However, due to the poor membrane permeability of modified target-specific fluorescent probes, drug screening for disease targets in live cells remains difficult. Here, we present a novel fluorescence-based drug screening strategy for intracellular live targets, utilizing cell-penetrating peptides to deliver non-permeable fluorescent probes. This strategy effectively facilitates the intracellular delivery of non-permeable microtubule paclitaxel-targeted fluorescent probes, with known drug experiments demonstrating its high sensitivity and accuracy. Through screening 58 unknown small molecules, two potential paclitaxel-targeting drugs were identified. These results highlight the significant potential of target probes with poor membrane permeability for screening disease-targeting drugs in live cells.

[AP-20] PIBM2024-0730-9

The effect of microgravity on changes of biochemical and mechanical signals in human lumbar intervertebral discs

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Abstract: Microgravity leads to back pain and spinal diseases in astronauts. More than 50% of astronauts report spine pain during space mission, with 86% of which occurred in the lower back. The incidence of disc herniation is about 4.3 times higher compared to matched control on earth, with the highest risk appeared in the first year after return to Earth. Studies have reported that microgravity is associated with intervertebral disc (IVD) degeneration, e.g., decreased proteoglycan synthesis rate and altered nutrients environment occurs during microgravity, which are significant indicators for disc degeneration. However, the biomechanical mechanisms underneath such associations are not clear. This study is aimed to quantitatively investigate the effects of microgravity on the biochemical and mechanical signals change in the IVD with a modelling approach.

Specifically, a three-dimensional finite element model was developed based on the multiphasic mixture theory. In simulation of the microgravity environment, the mechanical boundary conditions on the disc were altered. The glucose, oxygen, and lactate concentrations, as well as their metabolic rates, and glycosaminoglycan (GAG) synthesis rate, water content, and mechanical signals in the IVD under microgravity and gravitational conditions were quantitatively analyzed and compared. Our results showed that, the concentrations of glucose and oxygen increased in the IVD under microgravity condition, while the metabolic rates of glucose and oxygen as well as GAG synthesis rate decreased in microgravity compared to those at gravitational condition. In addition, the water content increased, and the proportion of solid matrix stress to total stress also increased in microgravity condition compared to those at gravitational condition. These changes in mechanical and biochemical signals contribute to a better understanding of the mechanisms through which microgravity impacts the health of the human lumbar IVD.

[AP-21] PIBM2024-0730-26

Mueller matrix imaging with improved resolution by deep learning method

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Abstract: Mueller matrix imaging is an effective way to extract optical properties of biomedical samples. Mueller matrix microscope based on dual division of focal plane (DOFP) polarimeters can realize fast full polarization imaging. However, the effective pixels of DOFP polarimeter is less than that of conventional CMOS image sensors, resulting in a lower resolution of DOFP microscope. Achieving both large field of view with a high resolution is a key challenge for this type of polarization imaging system. We propose a deep learning method to generate high-resolution Mueller matrix images from low resolution Mueller matrix images. Our system has a large field of view using low magnification objective lens with a high resolution, meaning a shortened scanning time for the whole slides. We applied our method to obtain Mueller matrices of HE-stained thyroid slides and Masson-stained rat tendon slides, which were imaged using 4x, 10x, and 20x lenses. The quantitative analysis results of MMPD decomposition demonstrated the improved signal-to-noise ratio (SNR) and enhanced resolution of dual DOFP imaging.

[AP-22] PIBM2024-0731-6

Optical trapping of a single virus in a host cell based on active-passive calibration for trap stiffness

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Abstract: Optical tweezers are considered a tool for trapping and measuring forces on single molecules and small particles. Current research mainly focuses on measuring force spectral information of particles suspended in solution. However, the viscoelastic environment within the cell presents additional challenges for the *in situ* calibration of force spectroscopy data. To address this issue, we used an active-passive calibration method to calibrate the optical trap stiffness in live cells through sinusoidal oscillation and spontaneous fluctuation responses. This technique was applied to *in situ* measurements of the optical trap stiffness and viscoelastic modulus of viruses inside a host cell. The results indicate that this method can measure the optical trap stiffness and related parameters of intracellular viruses at different frequencies. Moreover, we proceeded to confirm that using quantum dots-labeled viruses inside cells increased the stiffness of the viral optical trap similar to that in fluid. This provides more robust support for future force measurements and analysis of the transport mechanisms of viruses trapped within live cells using optical tweezers.

[AP-23] PIBM2024-0731-11

Qualitative analysis of caffeine in beverages based on Raman spectroscopy

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Abstract: Caffeine (1,3,7-trimethylxanthine) is an alkaloidal stimulant widely found in food additives. With the marked increase in the variety of caffeine-containing foods and beverages, caffeine has become the most commonly ingested pharmacologically active substance, and people are ingesting excessive amounts by ignoring the presence of levels in beverages and foods. Therefore, there is a great need to realize one's caffeine daily intake and the potential for caffeine addiction. Constructing a fast and convenient analyzing method is beneficial to prevention of caffeine addiction. Raman spectroscopy has the advantages of being fast and non-destructive with widely usage in various fields. In this study, the caffeine contaning beverages in the market of China were analyzed *via* a Raman spectrometer based with 785 nm excitation wavelength. The beverages contained about a total of 30 samples, including energy drinks, carbonated beverages, tea beverages, instant coffee, freeze-dried coffee and instant tea powder. Spectral data of caffeine standard was

collected. And the characteristic peaks at 554 cm^{-1}, 740 cm^{-1}, 1070 cm^{-1}, 1327 cm^{-1}, and 1698 cm^{-1} were identified as the qualitative standards. The raw spectral data of beverage samples were pre-processed with noise reduction and baseline correction. Then a qualitative model was constructed by classification methods such as principal component analysis and partial least squares discriminant analysis. Especially, the two model could identify Spirte (without caffeine) from other beverages. Classification discrimination was carried out using k-nearest neighbor classification (KNN) and support vector machine (SVM). The results of the two models exhibited a better classification of liquid samples. Thus, this study demonstrated that Raman spectroscopy combined with machine learning could achieve non-destructive, rapid and efficient qualitative detection of caffeine components in liquid beverages.

[AP-24] PIBM2024-0802-5

Identification method for prohibited drugs based on X-ray absorption spectroscopy and machine learning

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Abstract: This study explores a new method for identifying prohibited drugs using X-ray absorption spectroscopy (XAS) detection and machine learning algorithm. A laboratory-developed scientific equipment was employed to obtain X-ray absorption spectra of ten different chemical substances, including various isomers of prohibited drugs. Principal Component Analysis (PCA) was then applied to extract the spectral features, minimizing data redundancy. Subsequently, the Extreme Learning Machine (ELM) combined with the Sparrow Search Algorithm (SSA) was utilized for analysis. The results demonstrate that this method can accurately identify different prohibited drugs, even excelling in the automatic identification of isomers. This research offers a novel and promising technique for quick non-destructive drug detection.

[AP-25] PIBM2024-0805-2

Ratiometric Covalently Labeled Fluorescent Probes for Super-resolution Imaging of Mitochondrial HClO During Ferroptosis

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Abstract: Long-term dynamic visualization of the spatial distribution and concentration changes of mitochondrial hypochlorous acid (HClO) is of great significance for revealing the molecular pathogenic mechanism of ferroptosis-related diseases. Super-resolution microscopy provides strong technical support for subcellular level imaging. However, due to the lack of mitochondrial HClO fluorescent probes with high

mitochondrial labeling stability, low interference from environmental factors, and low spectral crosstalk, imaging them is still challenging. Herein, a ratiometric covalent mitochondrial HClO fluorescent probe (YM-P) with ultra-large Stokes shift was developed. The triphenylphosphine group and chloroacetyl chloride group modified YM-P can achieve mitochondrial covalent labeling, improve the stability of mitochondria labeling, and overcome the challenge of probe off-target in long-term imaging. The ratiometric fluorescence response of YM-P to HClO makes it immune to environmental factors, and the ultra-large Stokes shift gives it minimal spectral crosstalk. The results showed that YM-P could achieve long-term dynamic super-resolution imaging of mitochondrial HClO concentration and spatial distribution during ferroptosis. For the first time, it has been observed that changes in mitochondrial cristae precede alterations in HClO concentration, with the number of these cristae exhibiting a trend of initially increasing and then decreasing. This work provides a potential tool for exploring the molecular pathogenic mechanisms of ferroptosis-related diseases.

[AP-26] PIBM2024-0819-20

Expanding super-resolution imaging versatility in organisms with multi-confocal image scanning microscopy

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Abstract: Resolving complex three-dimensional subcellular dynamics noninvasively in live tissues demands imaging tools that balance spatiotemporal resolution, field-of-view (FOV) and phototoxicity. Image scanning microscopy (ISM), as an advancement of confocal laser scanning microscopy (CLSM), provides a two-fold 3D resolution enhancement. Nevertheless, the relatively low imaging speed has been the major obstacle for ISM to be further employed in in vivo imaging of biological tissues. Our proposed solution, multi-confocal image scanning microscopy (MC-ISM), aims to overcome the limitations of existing techniques in terms of spatiotemporal resolution balancing by optimizing pinhole diameter and pitch, eliminating out-of-focus signals, and introducing a frame reduction reconstruction algorithm. The imaging speed is increased by 16 times compared with multifocal structured illumination microscopy. We further propose single-galvo scan, akin to the Archimedes spiral in spinning disk confocal system, to ensure high speed ang high accuracy scan without galvanometer's inertial motion. Benefitting from its high photon efficiency, MC-ISM allows continuous imaging of mitochondria dynamics in live cell for 1000 frames without apparent phototoxicity, reaching an imaging depth of 175 μm. Noteworthy, MC-ISM enables the observation of the inner membrane (IM) structure of living mitochondria in Arabidopsis hypocotyl for the first time, demonstrating its outstanding performance.

[AP-27] PIBM2024-0820-5

The interaction between DNA and doxorubicin was studied by reflection interference spectroscopy

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Abstract: Reflective Interference Spectroscopy (*RIfS*) technology has been widely applied in the field of biomolecular sensing due to its real-time, non-destructive, and high-sensitivity advantages. This paper presents the design of a novel nano-biosensor based on RIfS technology and builds an integrated optical detection system that includes temperature control, molecular detection, and data analysis, achieving the detection of the interaction process between DNA molecules and doxorubicin (DOX). Initially, spectral information is collected based on the RIfS system, and the corresponding EOT spectrum is obtained using Fast Fourier Transform (*FFT*). By observing the shift of the EOT peak position, the binding process of DNA and DOX is sensitively monitored, with experimental results highly consistent with theoretical data.
The research findings of this paper have potential practical prospects in the field of label-free, online monitoring of biomolecular interactions.

[AP-28] PIBM2024-0831-1

The theoretical research on high-resolution CARS microscopy with multi-focal excitation

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Abstract: The CARS microscopy is a label-free microscopy with the inherent vibrational spectra of matter molecules to provide imaging contrast. The samples' molecular spatial distribution images can be acquired by point-wise scanning with tightly focused laser beams. In this research, a multifocal excitation high-spatial-resolution CARS microscopy with the optical field's modulation technique of two-dimensional optical lattices is proposed. The periodical two-dimensional optical lattices can be used as excitation source. The conditions of compressing the spatial distribution of each cell in two-dimensional optical lattices with the optical field's modulation are theoretically analyzed. On this basis, excitation processes of samples to generate the CARS spectral signals is theoretically analyzed with two-dimensional optical lattices, which meets the requirements of high spatial resolution. By optical field's modulation of two-dimensional optical lattices as the excitation source, the CARS microscopy is realized with the spatial resolution breaking through the optical diffraction limit. The system's 3D spatial resolution is theoretically investigated. Our theoretical analysis and simulation

research work provide a theoretical basis and guidance for the system structure design, method implementation and optimization of multifocal excitation CARS microscopy with high spatial and temporal resolution based on the optical field's modulation technique of two-dimensional optical lattices.

[AP-29] PIBM2024-0918-1

Strategies and basic applications of biosensing based on *Thermus thermophilus* Argonaute in gene diagnosis

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Abstract: The accurate and timely diagnosis is of great significance in point-of-care testing. Abnormal expression level of nucleic acids might be associated with cancer. Molecular biomarkers like cell-free DNA, cell-free circulating tumor DNA, microRNAs and exosome have been verified have the potential for disease monitoring, Therefore, highly sensitive and specific nucleic-acid-based strategies are critical for effective disease detection. *Thermus thermophilus* Argonaute(TtAgo) proteins have recently emerged as powerful and versatile nucleases for genome editing and molecular diagnosis. The programmable guide DNAs can be designed flexible according to the characteristics of TtAgo Herein, we developed an exponential amplification strategy based on TtAgo named EAgo which could achieve specific amplification of single base mutation. Furthermore, combining vent (exo-) polymerase and TtAgo which enable efficient and rapid amplification. We selected the EGFR L858R and microRNAs as target models. Our study explored the feasibility of linear and exponential amplification based on Ago respectively. We also explored the clinical application ability of this research on colorimetric sensing and lateral flow strip. The results suggest that the TtAgo can trigger efficient, highly specific amplification and distinguish let7a homologous family genes in miRNA. The lateral flow strip results show that the test line can be significantly enhanced in the presence of Ago. This study will provide new methods for the application of TtAgo in the field of biosensing and provide a new method for gene mutation detection.

[AP-30] PIBM2024-1007-1

Excited-states relaxation in FAD: the role of conformation states

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Abstract: We present the results of experimental and theoretical studies of excited state dynamics of flavin adenine dinucleotide (FAD) in water-methanol and water-ethanol mixtures as a function of alcohol concentration. The experimental studies have been carried out by recording time-resolved polarized fluorescence in FAD after excitation with short laser pulses using the time-correlated single photon counting

method. The results obtained have shown that in aqueous solution fluorescence decay in FAD could be presented as a sum of four exponents with decay times of 20 ps, 210 ps, 2.70 ns, and 3.85 ns. Molecular dynamics (MD) simulations and QM/MM calculations in water-methanol and water-ethanol mixtures have been carried out and revealed the existence of three distinct conformation groups of FAD: Stack I, Stack III, and Open, which differ by mutual positions of the adenine and isoalloxazine rings and interaction between them. A model has been developed for elucidation of the excited state dynamics in FAD and of the nature of the heterogeneity of the recorded fluorescence decay times. The model classifies several relaxation channels in FAD and suggests that the sub-nanosecond decay times of 20 ps and 210 ps both reflect fast fluorescence quenching due to electron transfer reactions in the vicinity of a conical intersection in the Stack III and Stack I conformations of FAD. It was also suggested that the nanosecond decay times of 2.70 and 3.85 ns were governed mostly by relatively weak non-radiative decay channels from the bottom of the lowest excited electronic state either via direct relaxation to the ground state, or via tunneling to a redox-pair excited state through potential barrier. The decay time of 2.70 ns was shown to refer mainly to folded conformations and the decay time of 3.85 ns to open conformations.

[AP-31] PIBM2024-1014-1

Imaging metabolic flow of water in plants with isotope-traced stimulated Raman scattering microscopy

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Abstract: Water plays a vital role in the life cycle of plants, participating in various critical biochemical reactions during both non-photosynthetic and photosynthetic processes. Direct visualization of the metabolic activities of water in plants with high spatiotemporal resolution is essential to reveal the functional utilization of water. Here, we applied stimulated Raman scattering (SRS) microscopy to monitor the metabolic processes of deuterated water (D_2O) in model plant *Arabidopsis thaliana (A. thaliana)*. Our work shows that in plants uptaking D_2O/water solution, proton-transfer from water to organic metabolites results in the formation of C-D bonds in newly synthesized biomolecules (lipid, protein, and polysaccharides, etc.) that allow high-resolution detection with SRS. Reversible metabolic pathways of oil-starch conversion between seed germination and

seed development processes are verified. Spatial heterogeneity of metabolic activities along the vertical axis of plants (root, stem and tip meristem), as well as the radial distributions of secondary growth on the horizontal cross-sections are quantified. Furthermore, metabolic flow of protons from plants to animals is visualized in aphids feeding on *A. thaliana*. Collectively, SRS microscopy has potential to trace a broad range of matter flows in plants, such as carbon storage and nutrition metabolism.

[AP-32] PIBM2024-1014-2

Surface Functionalized Gold Nanofluorescent Probes for Live-Cell Super-Resolution Long-Term Imaging of Endoplasmic Reticulum Dynamics

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Abstract: Endoplasmic reticulum (ER) stands as one of the most crucial subcellular structures within cells, participating in processes such as protein processing and modification. Its dysfunctional states are intimately linked to many diseases, including cancer and inflammation. Furthermore, the ER is also a highly dynamic subcellular structure, where not only its network undergoes rapid and continuous changes but also it interacts closely with mitochondria, lysosomes, and other organelles, collectively engaging in various physiological and pathological activities within cells. The advent of super-resolution microscopy has enabled us to surpass the resolution limits of traditional optical microscopes, revealing finer ER structures at the sub-micrometer level. However, long-term super-resolution fluorescence imaging of ER dynamics still necessitates the development of fluorescent probes with higher brightness and enhanced resistance to photobleaching. Herein, we harness the advantages of gold nanoparticle (GNP) fluorescent probes, which boast a large surface area and ease of modification. By decorating the surface of GNPs with the fluorescent dye Atto565, the cell-penetrating peptide fR8, and the targeting moiety Halo-tag, we constructed a GNP-based fluorescent probe (GNP-Atto565-fR8-CA) that exhibits high brightness, robust photobleaching resistance, and high stability. By modifying multiple Atto565 dyes, the GNP-Atto565-fR8-CA probe achieved a fourfold increase in fluorescence brightness and a threefold enhancement in photobleaching resistance compared to existing commercial fluorescent probes. The incorporation of the cell-penetrating peptide fR8 overcame the challenge of GNPs being readily trapped in vesicles, achieving a cytosolic delivery efficiency of 70%. The Halo-tag technology facilitated specific targeting to the ER. Using this probe, we successfully captured the expansion and contraction of tubular ER, ER-involved mitochondrial fission, and the "hitchhiking" behavior between the ER and lysosomes. This work provides a practical tool for investigating the ultrastructural features of the ER and the interactions among organelles.

[AP-33] PIBM2024-1015-1

Detection of prostate cancer combining Raman spectroscopy with multilayer perceptron

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Abstract: In the previous researches on medical diagnosis of SERS, the most common machine learning method was principal component analysis-linear discriminant analysis (PCA-LDA) , but this method had certain limitations and low classification accuracy. Therefore, this study compared surface-enhanced Raman spectroscopy (SERS) of plasma from prostate cancer (PC) patients and healthy controls using a deep learning method known as multilayer perceptron (MLP). First of all, the average spectrum and difference spectrum of the two are made to roughly compare the difference between them. Secondly, several raman positions with obvious characteristics are selected to conduct histogram comparative analysis. Finally, PCA-LDA algorithm and MLP algorithm are respectively used to diagnose the obtained experimental results, and visualization analysis is carried out in combination with figure. The final results showed that although the classification accuracy of PCA-LDA was also good for PC, the diagnostic results of MLP were better than PCA-LDA, and the sensitivity and specificity were also higher than PCA-LDA. This indicated that MLP algorithm combined with SERS improved the accuracy of early detection of prostate cancer, and was expected to be expanded in the early screening of other cancers, which had great potential in clinical application.

[AP-34] PIBM2024-1015-5

Raman Spectroscopy Enhancement Based on Deep Learning

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Abstract: Raman spectroscopy is a powerful analytical tool, but its practical application is often limited by the weak intensity of Raman signals, which are generated through Stokes shifts. Due to the low efficiency of Raman scattering, traditional Raman signals are inherently weak, necessitating enhancement methods to improve detection sensitivity. Conventional techniques such as Surface-Enhanced Raman Spectroscop and Stimulated Raman Scattering have been widely employed to amplify Raman signals. In this study, we propose a novel deep learning-based approach to directly enhance Raman signals without the need for external enhancement agents or complex equipment. Preliminary results using Rhodamine 6G as a test sample demonstrate the feasibility of this approach, indicating its potential for significantly increasing Raman signal intensity.

[AP-35] PIBM2024-1015-8

A Multifunctional Fluorescence Imaging Control System By LabVIEW

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Abstract: A multifunctional fluorescence imaging system called LMF-FLIM based on LabVIEW has been developed, capable of performing fluorescence scanning imaging, and fluorescence lifetime imaging (FLIM). The system utilizes software based on LabVIEW to control a data acquisition (DAQ) card, time-correlated single photon counting (TCSPC) card, and galvanometer, enabling point-scan imaging. The FLIM module integrates dynamic link libraries (DLLs) for galvanometer control, allowing simultaneous management of the galvanometer while outputting clock synchronization signals from the DAQ card as trigger signals for FLIM. This functionality facilitates TCSPC FLIM. Furthermore, by incorporating related DLLs and introducing a 3D sample stage, the system can manipulate the 3D sample stage to conduct fluorescence imaging at various depths, thereby generating 3D images of the samples and achieving 3D scanning imaging. Ultimately, the system seamlessly integrates LabVIEW software, confocal scanning system, DAQ card, 3D sample stage, and TCSPC card into a single platform for multifunctional fluorescence imaging. All imaging operations are executed within one software interface, which outputs image data for further processing. Compared to commercial FLIM systems that operate on multiple independent software platforms, our system minimizes unexpected errors and latency caused by inter-software communication and file transmission, successfully achieving multifunctional imaging.

[AP-36] PIBM2024-1015-10

Fusion protein localization predicted by AlphaFold2

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Abstract: Currently, rapid and accurate prediction of targeting expression of a fluorescent protein tagged fusion protein remains a great challenge. Molecular docking simulation methods have been widely used to

predict molecular binding targets in previous studies. However, these prediction methods rely on the existing protein structures and existed structural predictions, leading to an unsatisfied accuracy. Here, we combine Alphafold2 with molecular docking simulations to predict the targeting effect of fluorescent protein EGFP or mCherry fused to cytoskeleton protein. The prediction results showed that the fusion of mCherry with beta-actin did not affect its expression in the cytoskeleton. In contrast, the fusion of EGFP with beta-actin inhibited its efficient participation in the formation of the cytoskeleton. Subsequently, the corresponding actin-mCherry and actin-EGFP expression vectors were constructed and transfected into cells. The transfected cells were observed under a confocal microscope. The imaging results showed that actin-mCherry participated in the construction of the cytoskeleton, while actin-EGFP dispersed in the cytoplasm. This work demonstrated a method to predict whether the fusion of fluorescent protein with a target protein will affect its original targeting function, and provides a new approach for optimizing the design of fusion proteins.

[AP-37] PIBM2024-1015-11

FLIM Monitors Mitochondrial Responses to Microplastics in KYSE-150 cell

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Abstract: As plastic pollution escalates, microplastics—particles less than 5 mm—have attracted significant scientific attention. They arise from everyday plastic waste, microbeads in personal care products, and bottled water packaging, posing threats to ecosystems and health. Polystyrene (PS), a widely used plastic, can affect humans through absorption, ingestion, and contact. KYSE-150 cell, a human esophageal squamous cell carcinoma line, are frequently used in cancer research. Exposure to microplastics can alter the tumor microenvironment, impacting KYSE-150 cell behavior and interactions with neighboring cells, thereby influencing tumor progression and treatment responses. An in-depth exploration of the interactions between microplastics and KYSE-150 cell can provide crucial data for understanding the behavior of microplastics within biological systems and their impact on cancer development, thereby establishing a scientific basis for assessing the health risks associated with plastic pollution. In this study, we employed fluorescence lifetime imaging microscopy (FLIM) to observe the mitochondrial state, characterizing changes in the microenvironment of KYSE-150 cell under stress from polystyrene (PS) microspheres (approximately 100 nm

in diameter). As time progresses, the number of intracellular microplastic microspheres increases, the cellular metabolism rate accelerates, and the mitochondrial fluorescence lifetime increases. This approach reveals the mechanisms by which microplastics affect the immune system. The results demonstrated that PS microspheres could enter KYSE-150 cell, and after a period of co-culturing, the mitochondrial lifetime increased. This finding suggests that FLIM imaging is a rapid, non-destructive, and sensitive detection method suitable for the biological monitoring of microplastics, providing important insights into the interactions between microplastics and KYSE-150 cell.

[AP-38] PIBM2024-1016-2

Analyzing spatial distribution of multiple histone modifications in single cells and across the genome via super-resolution imaging

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Abstract: Histone modification plays an important role in various physiological processes through regulations of chromatin accessibility. However, its spatial distribution in the nucleus has not been well studied due to method limitations. The conventional methodology, relied on high-throughput sequencing technologies, can only resolve one-dimensional genome-wide distribution of histone modifications, but lacks the capability of capturing the spatial distribution and co-localization information of these marks in three-dimensional nucleus. Moreover, the traditional immunofluorescence staining approach for spatial study is limited by low resolution and multiplexing capability. Therefore, effective methods remain to be developed for acquiring the spatial distribution of multiple histone modifications within a single nucleus and across the genome. In our previous investigations, we successfully used Tn5 transposase to selectively label the open chromatin regions across the genome and visualize them via super-resolution imaging. In this project, we take advantage of pA-Tn5 fusion protein and specific antibodies to selectively label histone modifications. In combination with fluorescence in situ hybridization (FISH) and stochastic optical reconstruction microscopy (STORM), this platform can achieve super-resolution imaging of the spatial distribution of multiple histone modifications within a single nucleus and across the genome. We will further apply this technique to the investigation of spatial distribution patterns of histone modifications related to rare cell populations, which can provide novel imaging tools for studying epigenetic regulations and pave the way for the investigation of their mechanisms and biological functions.

[AP-39] PIBM2024-1016-3

Super-resolution analysis of the spatial distribution of 5hmC in single cell genome

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Abstract: The methylation and demethylation of genomic DNA play crucial regulatory roles in various physiological and pathological processes. Among them, 5hmC is a recently discovered product of DNA demethylation and has been shown to be closely associated with epigenetic reprogramming, aging and cancer progressing, yet little is known about its spatial distribution and function across the genome. It has been shown that the one-dimensional genome-wide distribution of 5hmC obtained from high-throughput sequencing is not sufficient to delineate its regulatory mechanisms and it is necessary to further explore the spatial distribution of 5hmC within the nucleus and its interaction with other epigenetic modifications. High-throughput super-resolution imaging technology has gradually become a powerful tool for studying spatial omics. In this project, we propose to selectively modify 5hmC in the genome and develop a whole-nucleus three dimensional super-resolution imaging technology to achieve super resolution analysis of the spatial distribution of genome-wide 5hmC. We will further apply this technique to the study of molecular regulatory mechanisms underlying 5hmC production, and importantly, the variations and functions of 5hmC during early embryonic development and tumor progression for the sake of exploring the diagnostic value of 5hmC for clinical usage.

[AP-40] PIBM2024-0808-1

Generation of non-diffractive optical beam by metasurface for optical imaging and a portable fluorescent lateral flow immunoassay platform for rapid detection of FluA

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Abstract: We have experimentally demonstrated that a strategy for generating broadband, long working and non-diffraction propagation distances, and high resolution Airy beams and beam arrays based on dielectric metasurfaces. Unlike the previous investigations which usually consider both amplitude and phase manipulations limiting available unit elements, pure phase manipulation enables direct phase additions of the cubic phase and the phase of a holographic Fresnel lens applied to the metasurface. Our work will open up an avenue for wider applications of Airy beams and beam arrays, especially for high-resolution optical imaging, optical tweezing with large penetration depths in live samples, as well as in the fields of parallel processing, for example, parallel laser printing and etc.

We have developed a lateral flow chromatographic immunoassay plat-form based on OPU for the rapid quantitative detection of FluA by lateral flow immunoassay test strips (ICTS). Through the integration of 3D-

printed components, miniaturized optical elements, and customized electronic control boards, we have successfully developed a portable, cost-effective LFIA platform. Our prototype platform exhibits the potential for rapid detection of infectious disease target analytes in vulnerable populations, owing to its sensitivity, specificity, and stability. This platform stands out as an accessible solution for a diverse user base, including non-professionals, students, and the elderly, due to its compact size, light weight, and low cost. Significantly, our work represents an effort in the field, as it marks the first reported instance of a portable LFIA detection platform using OPU for FluA detection. Furthermore, our proposed platform enables a seamless transition to detecting other types of fluorescent dyes by replacing the emission filter when the fluorescence excitation spectrum matches the three kinds of OPU laser diodes. Therefore, it is versatile, flexible, and able to cater to different research needs, especially within the realm of biomedicine.

Immunophotonics

[IP-1] PIBM2024-0730-13

Precision Engineering of Single Domain Antibody for Biomedical Imaging

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Abstract: Single domain antibody (sdAb), also called nanobody (Nb), is a small antibody fragment first discovered in *Camelidae*. It exhibits several encouraging properties not regularly found in full-sized antibodies, such as a very small size (~15 kDa), high stability, deep tissue penetration, renal clearance and low immunogenicity. These unique features make nanobody an appropriate and promising alternative for antibody-based imaging and therapeutics. However, antibody applications frequently necessitate the incorporation of additional groups, such as dyes, chelators, drugs, and other labels. Although random labeling methods that rely on endogenous cysteine or lysine residues in proteins are simple and widely used, they may lead to heterogeneous products with variable functionalization ratios, and sometimes a loss of targeting ability. Site-specific engineering strategies, such as enzyme-mediated methods and click chemistry, have gained huge interest in the industry and the research field. Herein, we describe a universal and facile strategy to produce homogenous nanobody molecular probes with ideal properties for biomedical imaging. Specifically, we first developed a kind of zwitterionic magnetic beads (MB) for the microbial transglutaminase (mTGase) immobilization. The immobilized enzyme (MB-mTGase) shows high catalytic activity and reusability, effectively simplifies the protein separation steps and reduces the loss of nanobody during purification. Using MB-mTGase and “click” strategies, dye, linker, photosensitizers, polyethylene glycol and other functional molecules can be easily and precisely conjugated to the specific site of nanobody. We demonstrated the fluorescent nanobody probes that enable targeted immunofluorescence imaging and PEGylated nanobody probes with improved circulation dynamics *in vivo*. In addition, glucose-incorporated nanobody probes with enhanced blood brain barrier (BBB) penetration and tumor targeting were yielded for brain tumor diagnostics and image-guided surgery. This study provides viable approach for the development of molecular probes in nanobiophotonics.

[IP-2] PIBM2024-0730-31

Nanomicelle hitchhiking neutrophils synergistically light-controlled CO release system for postoperative pancreatic cancer treatment

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Abstract: Pancreatic cancer is one of the common malignant tumors in the digestive system. It is called "the king of cancer" because of its high fatality rate and poor prognosis. Postoperative adjuvant chemotherapy is still the main clinical treatment for pancreatic cancer. However, previous studies have shown that patients with pancreatic cancer are highly resistant to chemotherapy drugs, leading to great challenges in its treatment. Therefore, finding ways to improve the sensitivity of pancreatic cancer to chemotherapy is the key to improving the survival rate of pancreatic cancer patients.. As a new cancer treatment strategy, gas therapy has been widely used in the research of anti-tumor therapy in recent years. Among them, carbon monoxide (CO), as an endogenous gas small molecule, has been found to not only damage mitochondrial respiratory metabolism and induce cell apoptosis, but also sensitize chemotherapy. Based on this, we constructed a CO release device based on NFC sensing, which can accurately control and realize the process of converting endogenous CO_2 into CO through NFC technology. In addition, we also reported an in situ hitchhiking strategy by encapsulating the anticancer drug doxorubicin (DOX) in liposomes and modifying the liposome surface with a neutrophil elastase-targeting peptide to enable it to target neutrophils (NEs) in the bloodstream. The drug-loaded nanomicelles hitchhiked to the inflammatory tumor site after surgery and then synergistically released CO gas small molecules, further killing tumor cells and inhibiting the growth of residual tumor cells. Therefore, in situ neutrophil hitchhiker delivery therapy combined with gas therapy can effectively inhibit the recurrence and metastasis of pancreatic cancer after surgery.

[IP-3] PIBM2024-0731-45

Wearable Ionic-Gel Photothermal Patch Enhanced with Electrostimulation for Diabetic Wound Therapy

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Abstract: The critical challenges of diabetic wound healing, including drug-resistant bacterial infections and obstructed blood flow, necessitate a novel approach. We developed a multifunctional wearable skin patch (PNITF), which incorporates photothermal and electrical stimulation therapies along with real-time monitoring capabilities. The patch employs a tannic acid-ferric complex (TA-Fe^{3+}) to catalyze the copolymerization of N-isopropylacrylamide (NIPAM) with a zwitterionic liquid (1-vinyl-3-carboxylate imidazole, IL). This ionic gel

rapidly forms in situ within 1 min, promoting strong tissue adhesiveness and self-healing properties, making it suitable for long-lasting attachment to human skin without hindering daily activities. The TA-Fe^{3+} complex enhances the gel's photothermal properties, allowing it to reach 60°C under 808 nm laser irradiation at 0.7 W/cm^2 within 10 min, effectively targeting drug-resistant bacteria. Additionally, the tannic acid in the PNITF gel inhibits bacterial growth and reduces blood sugar levels, proving effective against multidrug-resistant pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) and Escherichia coli (MDR E.coli). With its excellent electrical conductivity (0.02 S/m), the PNITF patch also serves as a platform for electrical stimulation therapy, further accelerating the wound healing process. Moreover, it enables real-time monitoring of human movement and body temperature. Given its high biocompatibility and cost-effectiveness, the PNITF skin patch represents a promising solution for diabetic wound therapy and may herald broader applications of ionic gels in the biomedical field.

[IP-4] PIBM2024-0815-1

Fluorescence Guided Sentinel Lymph Node Mapping Based on Biomimetic Indocyanine Green Nanoprobes

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Abstract: Indocyanine green (ICG) real-time fluorescence imaging has been widely used for visualizing tumor sentinel lymph nodes (SLN). However, its limitations include poor fluorescence stability, diffusion imaging, and concentration-dependent aggregation, which will hinder the accurate distinction between SLN and secondary lymph nodes (LN). Synthesize a biomimetic fluorescent probe (M@F127-ICG) coated with macrophage membrane which can implement high accumulation in SLN, enhanced fluorescence intensity, and the stability of ICG for rapid and accurate SLN detection. F127-ICG was synthesized via thin film hydration (TFH), and its optical and thermal stability, along with the in vivo lymph node (LN) targeting efficacy of F127 (DiR-BOA), were evaluated compared with free ICG, which shows improved fluorescence intensity and optical and thermal stability for LNs targeting. The macrophage membrane (MM) was extracted for the synthesis of M@F127-ICG, and the characterization along with the targeting capacity of M@F127 (DiR-BOA) was assessed in vitro macrophages and in vivo SLN. M@F127-ICG effectively encapsulates ICG, boosts its fluorescence intensity, and accumulates in SLN in vivo. The distribution of M@F127-ICG in draining LNs and its in vivo SLN tracing capability were dynamically monitored using a small animal in vivo imaging that indicated the fluorescence intensity of M@F127-ICG differentiates LNs and ensures effective retention in the popliteal LN, facilitating precise SLN detection. Additionally, the biocompatibility and in vitro cytotoxicity of M@F127-ICG were examined and confirmed M@F127-ICG exhibits excellent biocompatibility. The biomimetic nanoprobe M@F127-ICG enhances ICG's stability and fluorescence intensity while targeting LN-resident macrophages through homologous targeting by MM, thereby improving the specificity and sensitivity of SLN detection and offering a novel approach for SLN tracing.

[IP-5] PIBM2024-0630-1

A deep learning multi-organ segmentation method in low-dose CT images of mice for FMT/CT imaging

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Abstract: Fluorescence molecular tomography (FMT) can retrieve the 3-D distribution and concentration of fluorescent targets through tissues of several millimeters to centimeters in vivo. X-ray computed tomography (XCT) provides important anatomical structural prior information to assist FMT reconstruction and image fusion. By combining the advantages of both different imaging modalities, FMT/CT dual-modality imaging technology obtain more comprehensive and in-depth biological tissue structure and function information. It has been widely used in biomedical research such as early tumor detection, small animal disease models, and drug development. Given the necessity for multiple CT scans for contin uous in vivo observation spanning from several days to months, the system employs a reduced X-ray dose to minimize exposure. However, this approach results in low image resolution, which can hinder the acquisition of CT anatomical structural information. To address the limitations of low-dose CT data in our experimental setup, we introduce a multi-organ segmentation method for mouse images, leveraging deep learning algorithms to enhance the analysis of anatomical structures under reduced radiation exposure. Our method uses UNet as the backbone network, combined with the self-attention mechanism of transformer and enhanced skip connections to assist image segmentation in low-contrast situations. The composite loss function of CELoss and DiceLoss and the deep supervision mode are used to guide network training. We can obtain more accurate mouse organ anatomical structural information to better combine FMT imaging methods, thereby advancing the research of FMT/CT multi-modality imaging.

[IP-6] PIBM2024-0730-30

Light-triggered nanocarriers modulate mitochondrial metabolism for enhancing anti-tumor immune response

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Abstract: Dysfunctional mitochondria in tumor cells result cellular metabolic reprogramming, which is major element in tumor immune evasion. Therefore, normalization of mitochondrial function in tumor cells as an emerging target for improving the immunosuppressive tumor microenvironment (TME) in favor of tumor immunotherapy. Herein, a photosynergistic Mitochondrial metabolism nanoregulator (Mito-MNR) was constructed based on thylakoid (TK) membrane and Hollow mesoporous MnO_2 (HM) loaded with 3-

nitropropionic acid (3-NPA) to augment the tumor immune response by regulating the mitochondrial function of tumor cells. Under near infrared light (NIR) irradiation, TK balanced mitochondrial oxidative phosphorylation (OXPHOS) and glycolysis via producing NADPH and ATP, which significantly boosted the function of tumor-infiltrating cytotoxic T cells and restrained the polarization of M2-like macrophages. In addition, HM highly increased NADPH production through amplifying photosynthesis in thylakoids as an electron acceptor, and further facilitate the activation of stimulator of the interferon genes (STING) pathway by generating Mn^{2+} from MnO_2. Concurrently, 3-NPA decreased mitochondrial succinate dehydrogenase activity, which remarkably enhanced major histocompatibility complex class I (MHC-I) expression, increased tumor antigen presentation, and recruited more T lymphocytes. Overall, the developed Mito-NMR offer a reliable strategy to strengthen the immune response of tumors by photo-modulating tumor mitochondria to ameliorate in situ tumor metabolic-immune intrinsic response.

[IP-7] PIBM2024-0730-35

Regulation of lymph node infiltration and cholesterol metabolism confer enhanced nanovaccine-mediated antitumor effect

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Abstract: Nanovaccines have been widely used in clinical research due to their excellent ability to modulate the immune system and show significant potential in cancer prevention and treatment. However, effectively regulating antigen-presenting cells (APCs) to promote the proliferation of specific T cells, as well as efficiently infiltrating lymph nodes for antigen cytoplasmic delivery, remain key challenges in nanovaccine development. This study for the first time reveals that modulating cholesterol metabolism levels in dendritic cells (DCs) can significantly enhance DCs' ability to promote the proliferation of specific T cells and markedly improve antitumor immune efficacy. Based on this, we have innovatively developed a nanovaccine using PLA2000 as the primary material, named PLA-pyro-Co^{2+}. The resulting nanoparticles can efficiently adsorb labeled proteins and peptide antigens, and also co-deliver MeβCD, His-TATκ, and Toll-like receptor adjuvants. On one hand, the loaded MeβCD can precisely regulate DCs cholesterol metabolism, thereby enhancing the formation time of immune synapses between APCs and naive T cells, which significantly improves nanovaccine efficacy. On the other hand, the introduction of TATκ enables both efficient delivery of antigens within the lymph node parenchyma and cytoplasmic delivery. In tumor models of wild-type mice and humanized immune system-reconstructed mice, our study for the first time demonstrates that this novel nanovaccine has superior tumor inhibition efficiency compared to conventional vaccines. Furthermore, spatial transcriptomics and single-cell TCR/BCR sequencing analyses further confirm that the novel nanovaccine significantly enhances the body's antitumor immune response and high TCR-related abundance against tumor antigens. In summary, this innovative vaccine delivery platform provides a groundbreaking conceptual validation and potential therapeutic strategy for clinical translation in the field of cancer vaccines.

[IP-8] PIBM2024-0730-39

Microwave-triggered ROS Nanobombs Enhanced Ablation/Immunotherapy through Aggravating Ca2+ Homeostasis Perturbation and Capturing in Situ Tumor Antigens

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Abstract: Microwave ablation has become an important radical treatment method for hepatocellular carcinoma (HCC). However, the high recurrence and metastasis rate derived by incomplete ablation is still a bottleneck which restricts the long-term survival of patients. Previous studies suggest that in addition to inducing thermal effects, microwave is also capable of exciting media with specific compositions to produce ROS, or regulate cellular signaling pathways, exhibiting unique "non-thermal effects." Developing nanoparticles with microwave-responsive properties as exogenous microwave-absorbing media, and leveraging their efficient heat generation (microwave thermal effect) and ROS production (microwave dynamic effect) under microwave excitation is expected to enhance the clearance efficiency of primary liver cancer lesions and address the insufficiencies in the ablation of the "transitional zone." In this study, we developed a microwave-responsive nanoparticle by in-situ growth of ultra-small gold nanoparticles on mesoporous carbon nanospheres, which delivers the natural products, Erianin (MCN/Au@En). In addition to the thermal effect, MCN/Au@En nanocomposites can also be excited by microwave irradiation to produce ROS. Interestingly, we found that the regulation of calcium voltage-gated channels by the non-thermal effects of microwave fields, accompanied with the modulation of calmodulin by Erianin, can together promote calcium ion influx, thereby inducing ROS bursts in cells. More importantly, MCN/Au@En is able to improve the tumor immunosuppressive microenvironment post-ablation, and it effectively activates and maintains a robust immune response by capturing antigens and persisting at the tumor site for an extended duration. This strategy integrates microwave ablation with immunotherapy sensitization, providing a promising direction for the further development of clinical applications centered on microwave ablation.

[IP-9] PIBM2024-0731-4

Mechanistic exploration of tumor vaccine effects with radiation-derived microparticles targeting lymph node CD169^{+} macrophages

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Abstract: Tumor vaccines activate tumor-specific immune responses by delivering tumor antigens along with adjuvants to the lymph nodes. Irradiated tumor cell-derived microparticles (RMPs) can carry multiple tumor antigens and serve as an excellent vehicle for tumor vaccines. However, the application of tumor vaccines is constrained by the limited efficiency of RMPs targeting lymph nodes and their weak immunogenicity. This

study presents a genetically engineered RMPs that overexpresses OX40L co-stimulatory molecules (OE-RMPs), which derives from Lewis cells. OE-RMPs can target lymph nodes, after loading with ganglioside GM3 (OE-RMPs@GM3)， the natural ligand of CD169. Additionally. CpG adjuvant is loaded onto OE-RMPs@GM3 to enhance the therapeutic and preventive effects against tumors. This study shows that OE-RMPs@GM3@CpG can effectively target $CD169^{+}$ macrophages in lymph nodes by which to cross-present tumor antigens to $CD8^{+}$T cells. Furthermore, OX40L co-stimulatory empowers RMPs@GM3@CpG to proficiently elicit T cell immune responses, thereby increasing the abundance TCR counts in the blood of mice. In mice Lewis subcutaneous tumor model with CD169 macrophage-specific clearance, the anti-tumor effect of OE-RMPs@GM3 is significantly reduced. OE-RMPs@GM3@CpG combined with PD-1 has achieved effective anti-tumor effects in the treatment of Lewis subcutaneous tumors and Lewis-luc pleural fluid models in mice, and can effectively prevent the occurrence of tumors in prevention model. In summary, this study designes a powerful RMPs vaccine that can efficiently target lymph nodes, directly activating native T cells to exert robust therapeutic and preventive effects against tumors, providing a general strategy for personalized tumor vaccines.

[IP-10] PIBM2024-0810-3

Nanoscale arrangement of PD-L1 in breast cancer cells revealed by super-resolution microscopy

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Abstract: PD-L1, an immune checkpoint protein widely expressed in cancer cells, maintains tolerance of anti-tumor immunity through engagement with its receptor PD-1 in T cells. However, the spatial organization of PD-L1 on the plasma membrane remains poorly understood. In the present work, we employ stochastic optical reconstruction microscopy (STORM) super-resolution microscopy to reveal the nanoscale arrangement of PD-L1 on the membrane of MDA-MB-231 breast cancer cells. We thus show that PD-L1 distributes randomly on the membrane as monomers. STORM visualizes the variation of PD-L1 density upon drug modulation, including IFN-γ, 2-DG, and a new-found anti-cancer drug, simvastatin. Nevertheless, drugs do not affect the monomeric state of PD-L1 on the membrane. Using secondary antibody-induced crosslinking based on STORM, we further demonstrate high lateral mobility and clustering capability of PD-L1. Moreover, PD-L1 forms nanoclusters at cell-cell conjugate sites between MDA-MB-231 cells and Jurkat T cells. Overall, these results based on STORM extend our understanding of the nanoscale arrangement of PD-L1 on the membrane in breast cancer cells

[IP-11] PIBM2024-0816-1

Black phosphorus mediated photoporation: a broad absorption nanoplatform for intracellular delivery of macromolecules

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Abstract: Nanoparticle-sensitized photoporation for intracellular delivery of external compounds usually relies on the use of spherical gold nanoparticles as sensitizing nanoparticles. As they need stimulation with visible laser light, they are less suited for transfection of cells in thick biological tissues. In this work, we have explored black phosphorus quantum dots (BPQDs) as alternative sensitizing nanoparticles for photoporation with a broad and uniform absorption spectrum from the visible to the near infra-red (NIR) range. We demonstrate that BPQD sensitized photoporation allows efficient intracellular delivery of both siRNA (>80%) and mRNA (>40%) in adherent cells as well as in suspension cells. Cell viability remained high (>80%) irrespective of whether irradiation was performed with visible (532 nm) or near infrared (800 nm) pulsed laser light. Finally, as a proof of concept, we used BPQD sensitized photoporation to deliver macromolecules in cells with thick phantom tissue in the optical path. NIR laser irradiation resulted in only 1.3× reduction in delivery efficiency as compared to photoporation without the phantom gel, while with visible laser light the delivery efficiency was reduced 2×.

[IP-12] PIBM2024-0819-1

Photothermal-Gas Combination Therapy promotes Checkpoint Blockade Immunotherapy in Colon Cancer

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Abstract: Checkpoint blockade immunotherapy emerges as a potential cure of cancer, but the monotherapy suffers from a low response rate in the clinic. Photothermal therapy (PTT) that harvests light energy to ablate tumor is reported to activate tumor-specific immune response, meanwhile nitric oxide (NO) is considered to involve in immune regulation. We designed a multifunctional nanoplatform that enables photothermal-gas

combination therapy by conjugating indocyanine green (ICG) and s-nitrosoglutathione (GSNO) onto polyvinyl pyrrolidone (PVP)-coated gold nanoparticles (Au@ICG-GSNO). Upon near-infrared light (NIR) irradiation, Au@ICG-GSNO heats up the cancer cell and triggers NO release from GSNO, thus inducing apoptosis in the tumor. We found the combination of NO with photothermal treatment causes immunogenic cell death, which should synergize with checkpoint blockade immunotherapy. In the mouse colon cancer bilateral model, we observed complete eradication of light-irradiated tumors and suppression of distant untreated tumors in the Au@ICG-GSNO with anti-PD-1 group. We found promoted infiltration of CD8+ T cells in the untreated tumors in the Au@ICG-GSNO with anti-PD-1 group comparing to anti-PD-1 alone. We also detected significant increase of pro-inflammatory factors in serum, such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) after PTT-gas-immunotherapy treatment, indicating the successful activation of the immune response. The improved immunogenicity caused by Au@ICG-GSNO with anti-PD-1 group allows for efficient antigen capture and presentation, as evidenced by the increased infiltration of dendritic cell (DCs) into the tumor-draining lymph nodes (LNs). Therefore, phototermal-gas-immune checkpoint blockade combination therapy represent a new promising treatment of metastatic cancer.

[IP-13] PIBM2024-0819-4

An Adaptive and Self-Healing Hydrogel Powder for Integrated Optical Glucose Sensing and Therapy

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Abstract: Chronic wounds in diabetes are typically characterized by recurrent inflammation, susceptible infection, difficile vascularization, and poor real-time monitor of the healing process. An ideal wound dressing is required to be adaptive, protective, and capable of integrating multiple therapeutic modalities. However, current commercial dressings often have individual functions and struggle to achieve satisfactory therapeutic outcomes. Therefore, developing an integrated multifunctional dressing is a significant challenge in the treatment of diabetic chronic wounds. Herein, a novel adaptive, self-healing and antioxidant hydrogel powder was exquisitely designed based on dynamic cross-linking (3-acrylamidophenyl) boronic acid (APBA) with epigallocatechin gallate (EGCG) through boronate ester bonds. Then aggregation-induced emission (AIE) luminophore tetraphenylethylene (TPE) was grafted to the main chain via radical copolymerization interaction to monitor the glucose changes. Finally, nitric oxide (NO) donor S-nitroso-N-acetylpenicillamin (SNAP) was loaded in the core via physical blending to improve angiogenesis, termed as E-A-SNAP Powder. The reversible boronate ester bonds allowed the smart hydrogel to flexibly deposited on irregular and incompressible bleeding wounds without external conditions. Once absorption of tissue exudate, the powder rapidly formed a dense "intelligent scab" that providing necessary physical protection. With dynamic changes of glucose levels at the wound site, the boronate groups in the "intelligent scab" specifically bind to glucose, triggering the rearrangement of the boron polymer network. Simultaneously, the AIE moiety produced bright fluorescence

signals, enabling real-time monitoring of wound glucose levels and on-demand drug delivery. Additionally, the "intelligent scab" releases EGCG and SNAP to eliminate oxidative stress and promote angiogenesis by releasing NO, synergistically promoting the healing of diabetic chronic wounds. The *in vitro* experiments demonstrated that E-A-SNAP Powder effectively eliminates oxidative stress and reduces inflammatory responses. Furthermore, the *in vivo* experiments verified that E-A-SNAP Powder improves collagen deposition and tissue remodeling, accelerating scar-free healing. The E-A-SANP powder propose a new perspective strategy for theranostic dressings and has great potential in the field of diabetic chronic wound treatment.

[IP-14] PIBM2024-0819-11

Spatiotemporal co-regulation of lymph node resident and skin-derived dendritic cells inhibits tumor growth and metastasis

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Abstract: Cancer vaccines therapy is attractive systemic immunotherapies and herald a next immunotherapy frontier. However, it struggled to perform well in different individuals due to the heterogeneity of the tumor itself and low immunogenicity. Here, a tumor whole antigen vaccine induced by melittin lipid nanoparticles (α-M-NPs-TWA vaccine) was prepare to co-regulate lymph node resident and skin-derived dendritic cells (DCs) for enhanced tumor vaccine therapy. Tumor antigens could be bound to the α-M-NPs adjuvants and taken up by DCs and macrophages in injection situ and lymph nodes. Subsequently, the cellular immunity in the lymph nodes and systemic humoral immunity were activated by early vaccination, and the systemic anti-tumor specific immune response was further induced by the immune cascade reaction, thereby achieving an inhibitory rate of more than 90% for subcutaneous melanoma and distant lung metastases. Moreover, the α-M-NPs-TWA vaccine effectively inhibited the colonization and growth of brain metastases by increasing the number and activation of intracranial anti-tumor T cells and shaping M1 macrophage-biased polarization. In addition to the satisfactory prevention effect to the tumor in situ and therapeutic effect to the metastases, α-M-NPs-TWA vaccine can also delay or even inhibit the growth of established tumor. Therefore, α-M-NPs-TWA vaccine with the characteristics of low-cost, strong immunogenicity, personalization, highly efficiency has great application potential or combined with clinical surgical resection to remove systemic micro metastases.

[IP-15] PIBM2024-0819-15

Intravital molecular imaging reveals that the molecular events of immune response induced by intracellular antigens

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Abstract: The immune response induced by tumor antigen and specific antibodies targeting tumor antigen play an important role in the antitumor effect. Intracellular antigens are important components of tumor antigens. Improving the recognition and binding of intracellular antigen by changing the permeability of cell membrane has become an important means of tumor immunotherapy. In this work, mice were subcutaneously inoculated with tetramer far-red fluorescence protein (tfRFP) as an intracellular model antigen. B16 melanoma cells expressing tfRFP (tfRFP-B16) were injected *via* the spleen to construct a disease model of tumor liver metastasis. Through intravital molecular imaging and atomic force microscopy imaging, we found that the immune response triggered by intracellular model antigen tfRFP inhibited the occurrence and development of tumor liver metastasis, and then the immune clearance effect induced by intracellular antigen on liver metastatic tumor was found. The molecular mechanism involved in binding of intracellular model antigen tfRFP to antibody during liver metastasis was revealed. It provides a new idea and clinical immunotherapy strategy for developing tumor vaccines and specific antibodies against intracellular antigens.

[IP-16] PIBM2024-0819-26

Visualization study on polarization and movement patterns of macrophages

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Abstract: Macrophages are one of the important innate immune cell populations in the body, playing a crucial role in resisting tumor development. The plasticity and heterogeneity of macrophages result in different polarization phenotypes in tumor progressions. These characters increase the difficulty of targeting macrophage therapies. One hurdle is the inability to accurately track and evaluate the effects of targeted therapies. Imaging techniques provide a variety of powerful non-invasive tools for dynamically monitoring

biological processes. Here, we have developed a novel imaging method based on gene editing to track the different polarization states of macrophages. We validated the effectiveness of the method in RAW264.7 cells *in vitro*. After transfecting RAW264.7 cells with the constructed specific polarized plasmid kits, flow cytometry was used to select positive cells characterized by M1 polarization states, named M1 RAW264.7 cells. Furtherly, we evaluated the response of M1 RAW264.7 cells to M1-promoting cytokines. In the absence of cytokine stimulation, fluorescence is almost unobservable in M1 RAW264.7 cells. The fluorescence intensity was measured in 24 h, 48 h and 72 h after stimulation by 100 ng/ml LPS and 2.5 ng/ml IFN-γ. We observed a significant increase in fluorescence intensity over time by confocal microscopy. Meanwhile, we used flow cytometry to quantitatively analyze fluorescence intensity. The results showed a 4-fold and 14-fold increase at 24 and 48 hours, respectively. Moreover, we found that after 48 hours without cytokine stimulation, the fluorescence intensity of cells returned to the unstimulated level. These results demonstrate the effectiveness of the macrophage polarized plasmid kits and the sensitivity of M1 RAW264.7 cells. In the future, we will be able to use simple and low-cost fluorescence polarization imaging tools to track polarization phenotype changes of macrophages in disease and drug responses without the need for expensive antibodies and complex procedures.

[IP-17] PIBM2024-0828-1

The regulation of cerebral lymphatic drainage in the transverse sinus region of mouse brain

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Abstract: Cerebral lymphatic drainage is an important pathway for metabolic waste clearance in brain, which plays a crucial role in the progression of central nervous system diseases. Recent studies have shown that norepinephrine (NE) involved in the regulation of cerebral lymphatic drainage function, but the modulation mechanism remains unknown. In this study, we confirmed that NE rapidly reduced glymphatic influx and enhanced the meningeal lymphatic clearance. Moreover, transverse sinus (TS) was the vital region of cerebral lymphatic drainage regulation by NE. Further analysis revealed that NE inhibition could simultaneously enhanced in the glymphatic drainage and dorsal meningeal lymphatic drainage, mainly acting on the TS region. This study demonstrated that the cerebral lymphatic drainage system can be regulated by NE, with the TS region serving as the primary modulating site. The findings provide a potential regulatory target for the amelioration of neurological diseases associated with cerebral lymphatic drainage function.

[IP-18] PIBM2024-1015-6

Direct Visualization of Immune Status for Tumor-Infiltrating Lymphocytes by Rolling Circle Amplification

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Abstract: The immune status of tumor-infiltrating lymphocytes (TILs) is essential for the effectiveness of cancer immunotherapies. However, due to the diversity of immune status in TILs, cellular heterogeneity and the applicability to the clinic, it is still lacking effective strategies to meet clinical needs. We developed a novel immuno-recognition-induced method based on rolling circle amplification (RCA), namely immunoRCA, to in situ visualize the immune status of TILs in actual clinical samples. This developed immunoRCA method, in which, feature mRNAs were used as the biomarkers for the immune status of TILs, has a low fluorescence background, high sensitivity and specificity. The immunoRCA was able to efficiently evaluate the immune status of CD8+T cells regulated by activating or inhibiting factors, track the T cell type and immune status during in vitro expansion, and in situ visualize the number, location and immune status of TILs in clinical specimens.

[IP-19] PIBM2024-1015-9

Diagnosis of Minimal Hepatic Encephalopathy Based on Photoacoustic Imaging

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Abstract: Hepatic encephalopathy (HE) is a neurological complication caused by severe liver disease. Minimal hepatic encephalopathy (MHE) represents an early stage in the progression of HE, characterized by subtle symptoms and a lack of overt clinical manifestations and cognitive impairments. Nevertheless, there is currently a dearth of precise imaging techniques for the monitoring of MHE. To address this issue, the present study proposes a rapid and high-resolution photoacoustic imaging approach with the objective of evaluating structural and functional changes in the hepatic vascular system under conditions of minimal hepatic encephalopathy. In the present study, we established both acute and chronic MHE models and employed dual-wavelength photoacoustic imaging technology to assess liver blood oxygen saturation and

the metabolic capacity for indocyanine green (ICG). The results demonstrated the presence of hyperammonemia in both types of MHE models, accompanied by notable abnormalities in liver function. In the acute MHE model, significant alterations in the structure of the hepatic lobules were observed, accompanied by a marked decrease in liver blood oxygen saturation. In contrast, the chronic MHE model exhibited notable morphological alterations in the liver, accompanied by a pronounced decline in the metabolic capacity for ICG. In particular, in the acute MHE model, there was a notable decline in liver blood oxygen signals over the course of five consecutive days, which was significantly different from that observed in the control group. In the chronic MHE model, the metabolic time for ICG was significantly prolonged, extending from 10 minutes to 30 minutes, which indicated a worsening degree of liver function impairment. In conclusion, multi-wavelength photoacoustic tomography technology shows considerable promise in assessing the drainage dynamics of the hepatic vascular system in the context of hepatic encephalopathy, offering vital support for the early detection and treatment of this condition.

Neurophotonics

[NP-1] PIBM2024-0729-1

A high-throughput image preprocessing method for Array-fMOST data using differential-guided filtered convolutional neural networks

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Abstract: High-throughput mesoscopic-level optical imaging technologies, exemplified by array fluorescence microscopy optical sectioning tomography (array-fMOST), have significantly improved the efficiency of acquiring mesoscopic datasets of the mouse brain. However, due to limitations in the field of view, the image strips obtained by these techniques often require further preprocessing steps, such as section stitching, artifact removal, and effective signal area cropping, to meet the needs of subsequent analysis. A single set of raw imaging strips of a mouse brain array acquired at a resolution of 0.65 × 0.65 × 3 μm^3 can reach up to 220TB in size. Additionally, the cropping of the outer contours of each mouse brain in these separate preprocessing steps still relies on manual visual inspection, which is resource-intensive in terms of computational resources and labor costs. In this study, we first developed a Deep Differential Guide Filter (DDGF) convolutional module by combining the multi-scale iterative differential guidance filtering principle with deep learning. This module effectively enhances image details while filtering out background noise. We then integrated DDGF with the U-Net network to design a lightweight automatic segmentation method for mouse brain arrays. Testing on our first established array mouse brain dataset yielded a Dice score of 0.92 and a Precision score of 0.98. Based on the data characteristics, we further used the minimum bounding rectangle calculation algorithm in connectivity analysis to automatically identify the specific locations of each mouse brain. Additionally, we optimized the overall processing workflow by establishing an automated high-throughput preprocessing pipeline, which is data stream-efficient and utilizes MPI parallel computing based on a cluster. This pipeline reduces the average preprocessing time for a complete mouse brain dataset to just 1.1 hours, increasing labor efficiency by 25 times and overall data processing efficiency by 2.4 times.

[NP-2] PIBM2024-0729-21

Blood oxygenation imaging through transparent cranial window using laminar optical tomography

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Abstract: Imaging cerebral blood oxygenation in rats provides critical insights into neural activity and brain disorders, thereby enhancing our understanding of brain physiology and facilitating the development of therapeutic interventions. Long-term monitoring of disease progression and intervention effects necessitates the use of a transparent cranial window on the skull to create an observation window. However, the scatter and absorption coefficients of the transparent cranial window differ from those of the underlying cerebral tissue, thereby decreasing penetration depth and reducing imaging quality. This study utilizes laminar optical tomography (LOT), which captures off-axial reflected light to image deeply. An 8-channel PMT is used, with the first channel detecting axial reflected light, while the remaining seven channels detect off-axis scattered light. Continuous-wave lasers at 488 nm and 520 nm are employed simultaneously to incident light into the cerebral tissue, monitoring changes in cerebral blood oxygenation. Results indicated that the cerebral vasculature imaged by channels 2 to 8 was clearer than that in channel 1. Following hypoxic stimulation, changes in tissue blood oxygenation are also observed in these channels. This system demonstrates robust imaging capabilities and the ability to resolve blood oxygenation changes under the constraints of a cranial window, showcasing its potential applications in studying cerebral hemodynamics.

[NP-3] PIBM2024-0731-35

Develop a compact six-axis positioning stage for high-precision multi-color fluorescence simultaneous coplanar imaging

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Abstract: In situ imaging of various types of fine biological structures at the single-cell level, and exploring the relative relationships between these fine structures with accurate annotation of whole-organ cytoarchitecture is highly desired in biomedical research. To achieve simultaneous coplanar acquisition of multi-color fluorescence signals, spatial alignment of the focal plane of each imaging channel with sub-micron precision is required, which is a huge challenge in compact microscopy systems. Thus we develop a parallel six-axis positioning stage based on the kinematic coupling principle. We propose an optimized design method to achieve the maximum workspace in a limited installation space, i.e., a working space of 1 cm cubic within an installation space of 15 cm cubic. We propose a kinematic pre-compensated strategy under open-loop control to reduce the impact of machining and assembly errors, which is capable of achieving about 1.0 μm positioning precision without positional feedback. Considering the stability of long-time continuous imaging, we further optimized the preload design to enhance the stage's ability to resist external interference. Integration of the developed stage with fluorescence micro-optical sectioning tomography (fMOST) system, we have achieved precise co-localization acquisition of multiple microstructures of whole organs. Overall, this novel high-precision six-axis positioning stage provides technical support for the synchronized and coplanar detection of multicolor fluorescence.

[NP-4] PIBM2024-0731-52

Weakly Supervised Iterative Neuron Image Identification Algorithm

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Abstract: At the mesoscale level, the data volume of mouse brain images can reach the level of 10TB, while that of the human brain can reach the astonishing level of several dozen PB. Recognition and analyzing the morphology of neurons from massive brain image data is a complex and challenging task. Currently, traditional machine learning methods suffer from poor transfer and generalization ability, while deep learning-based algorithms lack precise and rich image annotation datasets, resulting in problems such as overfitting and weak generalization ability. This article proposes a weakly supervised neuron recognition method based on deep learning, which requires only a small amount of labeled data, and can obtain accurate recognition results of a large amount of unlabeled data through iterative strategies, which has strong generalization capabilities and minimizes human participation. This method has been experimentally verified on brain image big data such as fMOST and BigNeuron, with recognition accuracies of F1 scores of 0.9247 and 0.8318, respectively, which are better than other compared neuron recognition algorithms.

[NP-5] PIBM2024-0819-7

High-efficiency photoacoustic microscopy for ultrafast hemodynamic imaging

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Abstract: Understanding brain functions requires visualization of cerebral hemodynamics with a high spatiotemporal resolution. Recent advances utilize various scanning schemes to promote the imaging speed of photoacoustic microscopy for label-free hemodynamic imaging. However, due to the insufficient utilization of laser pulses, recording cerebral hemodynamics with a satisfactory spatiotemporal resolution still remains a challenge. Here, we employ a 3-axis optical scanner and an optically compatible acoustic scanner to develop a high-efficiency photoacoustic microscopy (HePAM) for the investigation of hemodynamics in the cerebral cortex. The scan engine provides an ultrafast B-scan rate of up to 1.6 kHz. We demonstrate its capability in

flexible imaging of specific regions of interest (ROIs) to capture hemodynamic responses in whole cortex, hemisphere, and arbitrary single blood vessel. HePAM also enables convenient intensity-based analysis of vasomotion dynamics and cerebral blood flow velocity for hemodynamic investigation.

[NP-6] PIBM2024-0819-25

Multi-region hemodynamic imaging in freely behaving mice with wearable optical coherence tomography

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Abstract: Real-time monitoring of cerebral hemodynamic changes under natural physiological conditions is critical to facilitating neurovascular research. The development of wearable optical imaging technology provides the opportunity to perform brain hemodynamics imaging in freely behaving mice. However, simultaneous high-resolution imaging of multiple brain regions remains challenging due to space constraints and the cumbersome weight of the equipment. Here, we present a miniature optical coherence tomography microscope (mini-OCT) optimized for micro-optical scanners and opto-mechanical design. The mini-OCT probe has a maximum scanning speed of 400 kHz, with about 10 μm lateral resolution and a large field of view (FOV) of 3×3 mm^2, allowing easy mounting and stable imaging in freely behaving mice. With its compact and lightweight design of 0.44 g, mini-OCT enables be implanted in multi-region on a mouse brain simultaneously. We used the mini-OCT to record multi-region cerebral hemodynamics and behavior change during the acute ischemic phase after photothrombotic stroke.

[NP-7] PIBM2024-0820-8

Optical Coherence Tomography-based Robotic Platform for Automatic Craniotomy

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Abstract: Neuroscience, rapidly advancing as a premier discipline of the 21st century, leverages animal models as a pivotal tool for demystifying brain and neural functionalities. Central to this endeavor, optical imaging technology emerges as a cornerstone, facilitating groundbreaking research. Nevertheless, its limited depth penetration poses challenges, necessitating the creation of optical cranial windows to achieve detailed, high-fidelity observations of brain activities. Traditional approaches for preparing these cranial windows, however, encounter numerous obstacles: they are skill-intensive, time-consuming, and challenged by unpredictably low success rates, thus impeding progress in animal neuroscience studies. To address these issues, we present an innovative surgical robot platform driven by Optical Coherence Tomography (OCT). This platform, enhanced by the precision imaging capability of OCT's three-dimensional transcranial imaging, meticulously guides the drilling process to make cranial windows with greater efficiency and a markedly higher

success rate. Our methodology harnesses OCT for gathering detailed tomographic data of the mouse skull, accurately segmenting its surfaces to ascertain the optimal drilling parameters. A bespoke, high-precision, three-axis milling platform then executes the craniotomy with unparalleled accuracy. Following the precise excision of the skull piece, a glass window is seamlessly integrated into the craniotomy site. We demonstrated the ability of the system by performing glass cranial window surgeries on five mice and a larger cranial window surgeries on an additional two mice. Further, we performed OCT angiography and OCT velocimetry measurements with the animals and show that the prepared craniotomy is good for OCT image beyond 14 days. This blend of advanced imaging and robotic precision provide a new tool for animal-based neuroscience research.

[NP-8] PIBM2024-0820-22

Design of an open-source program for fluorescence signal correction based on the absorption spectrum of hemoglobin

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Abstract: Wide-field fluorescence imaging has been extensively employed to investigate the interplay of neural activities across various regions of the brain. However, non-neuronal hemodynamic signals often contaminate the imaging outcomes, necessitating the implementation of hemodynamic correction as a pivotal step in data analysis. While numerous methodologies exist for hemodynamic correction, such as alternating blue-violet light excitation for non-neuronal signal subtraction and dual-reflectance measurement, they either remain confined to internal use or encompass additional functionalities that impose significant demands on storage capacity and computational power. This paper presents a dedicated fluorescence correction program based on the dual-reflectance measurement method, which exhibits the following merits: (1) User-Friendliness: A tailored CSV file is designed to facilitate parameter input, allowing users to populate corresponding parameters by their names in a straightforward manner. This approach enhances the accessibility and usability of the program for a broad range of researchers. (2) High Modularity: The program is designed with a streamlined focus, exclusively retaining the function of fluorescence correction, thereby minimizing unnecessary resource consumption and maximizing overall efficiency. (3) Flexibility and Extensibility: By offering flexible configuration options and scalable interfaces, users are empowered to adjust the fluorescence correction parameters and image data dimensions according to their specific research requirements. This adaptability ensures that the program can cater to the diverse needs of researchers, fostering a personalized user experience. Collectively, the program developed in this study represents a novel approach to fluorescence correction in wide-field imaging, offering a user-friendly, resource-efficient, and highly customizable solution tailored specifically for investigating neural activities while mitigating the influence of non-neuronal hemodynamic signals.

[NP-9] PIBM2024-0913-1

Rational design of Aβ fluorescent probe with NIR-II emission for early Alzheimer's disease diagnose

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Abstract: Amyloid-β (Aβ) species (Aβ fibrils and Aβ plaques), as one of the typical pathological markers of Alzheimer's disease (AD), plays a crucial role in AD diagnosis. Currently, some near-infrared I (NIR I) Aβ probes have been reported in AD diagnosis. However, they still face challenges such as strong background interference and the lack of effective probe design. In this study, we propose molecular design strategy that incorporates CN group and amphiphilic modulation to synthesize a series of amphiphilic NIR I Aβ probes, surpassing the commercial probe ThT and ThS. Theoretical calculations indicate that these probes exhibit stronger interaction with amino acid residues in the cavities of Aβ. Notably, the probes containing CN group display the ability of binding two distinct sites of Aβ, which dramatically enhanced the affinity to Aβ species. Furthermore, these probes exhibit minimal fluorescence in aqueous solution and offer ultra-high signal-to-noise ratio (SNR) for in vitro labeling, even in wash-free samples. Finally, the optimal probe DM-V2CN-PYC3 was utilized for in vivo imaging of AD mice, demonstrating its rapid penetration through the blood-brain barrier and labelling to Aβ species. Moreover, it enabled long-term monitoring for a duration of 120 minutes. These results highlight the enhanced affinity and superior performance of the designed NIR I Aβ probe for AD diagnosis. The molecular design strategy of CN and amphiphilic modulation presents a promising avenue for the development Aβ probes with low background in vivo/in vitro imaging for Aβ species.

[NP-10] PIBM2024-0919-2

Mesoscopic Dissection of the Organizational Logic in One Cortical Connection Hub: Retrosplenial Cortex

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Abstract: The cerebral cortex with the intricate circuitry, is the epicenter of higher brain functions, including perception, cognition, and consciousness. Its intricate structure of multiple layers and interconnected neurons enables it to perform sophisticated tasks. Understanding the organizational logic underlying these connections is crucial for deciphering the neural operational mechanisms. As a hub connecting the cortex and multiple

subcortical regions, the retrosplenial cortex (RSP) is closely associated with a variety of cognitive functions, including spatial navigation, self-referenced computations, and emotion. Our previous studies revealed bidirectional connectivity circuits among RSP, thalamus, and other brain regions. However, the complexity of the connectivity network makes it difficult to explain the regulatory mechanisms with long-range and local circuits. Here, with the fluorescence micro-optical sectioning tomography (fMOST) system, we obtained the whole-brain continuous datasets with a resolution of 0.32 × 0.32 × 1 μm^3. Subsequently, the morphology of individual neurons was reconstructed, which showed distinctive preferential connectivity properties. These works of cortical architecture are of the paramount importance, offering insights into the very essence of intelligence and the human experience.

[NP-11] PIBM2024-0725-3

Performance Evaluation and Major Challenges in Automated Neuron Reconstruction

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Abstract: The study of single-neuron morphology is crucial for understanding the brain's complex structure. Despite advancements in optical microscopy, achieving fully automated and highly accurate neuron reconstruction remains elusive, often requiring substantial manual corrections. This limitation impacts reconstruction speed and increases costs. Our research systematically evaluated existing automatic neuron reconstruction algorithms using mouse brain data obtained through AAV labeling and the fMOST imaging system. Based on the test results, we selected several leading methods, localized their reconstruction errors, and analyzed the principal factors contributing to these errors. The study revealed major challenges in neuron reconstruction, including weak signal intensity, fiber crossing structures, and parallel adhesion issues. We compiled a "High-Difficulty Dataset" containing various challenging cases for algorithm development, testing, or data-driven method training. This research provides valuable references and directions for the development and refinement of neuron automatic reconstruction algorithms.

[NP-12] PIBM2024-0729-10

Distinct spatiotemporal dynamics of inhibitory neurons in the cerebral cortex of Parkinson's mice

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Abstract: Substantial evidence indicates that the pathological mechanisms of Parkinson's disease extend beyond the nigrostriatal dopaminergic pathway, encompassing the cortico-basal ganglia-thalamo-cortical neural circuits. However, our comprehension of how Parkinson's disease alters cortical mesoscale dynamics remains incomplete, partly due to the predominant focus of prior studies on isolated changes within individual brain regions. In this investigation, we established a Parkinson's disease model in mice by inducing nigrostriatal and striatal dopamine depletion using the neurotoxin MPTP. Specifically, we employed wide-field calcium imaging in non-anesthetized, head-fixed mice, utilizing neuron type-specific Cre promoters and GECIs for calcium fluorescence imaging. This approach enabled us to scrutinize the distinctive spatiotemporal dynamics of complex inhibitory neurons and investigate alterations in macroscopic information flow within the cerebral cortex under Parkinsonian conditions. Our findings underscore that the dynamics of inhibitory neurons in Parkinson's disease are influenced by multiple factors, including neuron type, brain region, and disease progression stage. Notably, we observed a preferential increase in cortical macroscopic information influx from lower-order cortical regions in the PD state. These insights contribute to a deeper understanding of the neuropathophysiological mechanisms underlying Parkinson's disease.

[NP-13] PIBM2024-0729-14

The pH-sensitive Aβ aggregate intelligently turn-on fluorescent ratio probes to visualize the pH microenvironment caused by lysosomal damage around Aβ plaques

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Abstract: Plaques formed by the deposition of β-amyloid (Aβ) in the brain are the most obvious in the pathological changes of Alzheimer's disease (AD). Here, in order to obtain an Aβ aggregate probe with good affinity and intelligent activation, a multi-level intelligent screening was designed, and the probe named QD was finally obtained. The fluorescence of QD after binding to Aβ aggregates is due to the steric hindrance effect. QD can recognize Aβs at the protein level, with an affinity two orders of magnitude higher than the gold standard dye THT, with a Kd of 33.91 nM, and can recognize and dynamically detect the amyloid fibrillation process in vitro, and identify Aβ plaques at the in vivo level of 5×FAD model mice. In addition, we found that the fluorescence ratio of QD binding to Aβ aggregates increased with the increase of pH, and the Green/Red (G/R) ratio increased. We applied this strategy to show that as AD disease worsens, the G/R ratio gradually decreases, indicating that the pH microenvironment around the plaque decreases. By exploring at the cellular and tissue levels, it was found that the decrease in the pH microenvironment around Aβ plaques is caused by proton leakage caused by damaged lysosomes in cells. These results suggest that the development and research process of QDs expands the current development platform of small molecule probes for Aβ

aggregates, and that this fluorescence ratiometric probe helps to understand disease progression from multiple perspectives and develop appropriate treatment strategies.

[NP-14] PIBM2024-0730-5

Enhanced cortical activation in the ipsilesional motor cortex of subacute stroke patients for lower-limb rehabilitation: evidence from a functional near-infrared spectroscopy study

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Abstract: Impaired gait in stroke survivors is associated with decreased functional independence. Here, this study aimed to evaluate the effectiveness and cortical activation patterns associated with unilateral lower-limb robot-assisted overground gait training using functional near-infrared spectroscopy (fNIRS), and to explore the relationship between the neuroplastic changes and lower-limb motor recovery in subacute stroke patients. Forty patients were recruited and randomly assigned to groups for robot-assisted training (RT group) and conventional training (CT group). All outcome measures were assessed at the baseline (T0), 2nd week (T1) and 4th week (T2) of treatment. The primary outcome was the difference between the groups in the change from baseline on the Berg Balance Scale (BBS) at T2. Secondary measures included changes in the Fugl-Meyer Assessment of lower limbs (FMA-LE), the Functional Ambulation Category (FAC), and cortical activation assessment with fNIRS. A total of 36 patients completed the study. Clinical outcomes, including the BBS, FMA-LE, and FAC scores, improved after 4 weeks of training in both groups, with significantly better BBS ($p = 0.018$), FMA-LE ($p = 0.021$), and FAC ($p = 0.010$) in the RT group than in the CT group. Enhanced cortical activation was observed in the ipsilesional motor cortex in the RT group, with a statistically significant increase in cortical activation laterality of the premotor and supplementary motor areas at T2 compared to T0 ($p = 0.042$) and T1 ($p = 0.019$). Furthermore, significant negative correlations were observed between delta FMA-LE and the changes in cortical response at the contralesional motor-related areas ($p < 0.05$). These findings revealed that robot-assisted overground gait training showed more advantageous improvements in gait and balance functions. The robot-assisted training may augment gait and balance recovery in patients with subacute stroke by modulating the cortical response related to the ipsilesional motor areas and its related functional network.

[NP-15] PIBM2024-0730-28

NIR-II fluorescence lifetime mesoscope

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Abstract: The fluorescence imaging in the second near-infrared (NIR-II) window is an emerging imaging technology that has the advantages of high tissue penetration depth and high signal-to-noise ratio. With the continuous development of NIR-II dyes and detector technology, NIR-II imaging technology and applications are booming. However, it is difficult for the existing NIR-II imaging technology to meet the requirements of large imaging field of view, high spatial resolution, large penetration depth and tomography capability at the same time. In order to overcome these limitations, we present a novel NIR-II fluorescence mesoscopy system based on the f-θ scanning scheme and confocal detection. Meanwhile, we add function of the fluorescence lifetime detection to obtain insight into the interactions between the fluorophore and its environment. We use the system to achieve NIR-II high-resolution imaging of cerebral blood vessels in non-craniotomy mice. The results show that the system not only has the ability to distinguish a single blood vessel, but also has a large imaging field of view, and also has the ability of three-dimensional tomography, which provides a new tool for the study of deep blood vessels.

[NP-16] PIBM2024-0730-29

Circuit mechanism underlyting the aging vulnerability of individual neuron

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Abstract: Aging is a systemic change in which bodies, organs and cells undergo degenerative changes. However, the aging process has great heterogeneity, and the aging speed is inconsistent in different bodies, organs or types of cells. For example, in the neurodegenerative disease such as Alzheimer's disease, cholinergic neurons in the basal forebrain are the first to suffer damage and loss, while other types of cells are relatively stable, a phenomenon known as selective vulnerability of neurons. What is the mechanism responsible for the selective vulnerability of neurons? Current hypotheses involve local environmental factors and long-range circuit factors, including age-related protein, peripheral glial cells and toxic protein accumulation, as well as the influence of input brain regions and projection targets. Therefore, to study the damage mechanism of neurons, it is necessary to conduct comprehensive analysis the local and long-term multi-factor from mesoscopic level. With the continuous development of high-resolution, large-range imaging technology, Fluorescence micro-optical sectioning tomography (fMOST) is helping to study degenerative diseases. In order to realize multi- factor in situ detection of neurons, this paper used Array-fMOST to collect serial slices in the imaging process, combined with multi-slice batch dyeing tool and two-dimensional slice registration software, which can realize simultaneous dyeing and rapid rinsing of batch slices. Moreover, the

staining information obtained from slices after imaging has the advantage of registering to 3D data set to obtain spatial coordinate features. In this study, cholinergic neurons in the basal forebrain were taken as an example, and the cell coordinates, local environment and circuit structure map of individual neuron were obtained at the same time, and the mechanism of neuron circuit damage was analyzed from the perspective of mesoscopic multi- factor, which also provided a new idea for further research on the treatment of degenerative diseases.

[NP-17] PIBM2024-0730-40

Single-neuron and whole-brain mapping of the arcuate fasciculus in macaque monkeys: insights into human homologous organization

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Abstract: The traveling courses and connectivity profiles of the arcuate fasciculus (AF) pathway in nonhuman primates have been a topic of debate. The extent to which its whole-brain organizing principles diverge from the human homolog is still unclear. Here we employed a viral-based genetic labeling strategy in macaque brains alongside fluorescence micro-optical sectioning tomography to develop a cross-scale method for single-neuron tracing of AF, and compared with brain-wide tractography derived from 11.7T diffusion MRI data. Using 7.0T diffusion MRI data from humans, we further launched a spectral embedding analysis for an interspecies comparison of the AF connectomes. Our results indicate that the macaque AF originates from the temporal-parietal area, traverses the auditory cortex and parietal operculum, extends through areas 45, 44, and 12 in the prefrontal cortex. Low-dimensional embedding representations revealed comparable AF connectivity profiles between the auditory cortex and temporal-parietal areas in both species. Notably, the human AF exhibits a more extensive expansion into the middle temporal gyrus, with increased connectivity leading to human-specific differences, especially pronounced in the prefrontal cortex and parietal operculum. These findings highlight the critical role of AF connectome expansion and differentiation in the development of human language capabilities.

[NP-18] PIBM2024-0731-5

Simultaneous multicolor line-confocal imaging based on line-illumination off-axis coding and linear decoding with PSF

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Abstract: Line-confocal imaging is widely used in high-resolution imaging of large-size biological samples because of its outstanding imaging speed and quality. To meet the demand for simultaneous imaging of multiple fluorescent markers, conventional multicolor line-confocal imaging uses beam-splitting devices to project different fluorescent signals onto separate detectors for parallel acquisition. However, this results in the number of simultaneous imaging channels being limited by the number of detectors and increases the cost and complexity of the imaging system. Here, we propose a novel simultaneous multicolor line-confocal imaging method that can effectively extend the multiplexing capability of line-confocal imaging. By off-axis encoding of multicolor line-illumination beams, the encoded mixed images of multiple fluorophores can be acquired on a single detector, and the PSF linear decoding algorithm is proposed to reliably reconstruct the monochromatic images of each fluorophore. Simulation and experimental results verified that this method was able to expand the number of simultaneous imaging channels on a single detector from 1 to 4 without sacrificing the imaging speed. Furthermore, the potential of this method to be applied to microbial community studies was demonstrated by classifying and counting mixed bacterial samples. We anticipate this method to serve as a cost-effective and reliable multicolor imaging solution to help researchers understand the structure and function of organisms more systematically, accurately, and efficiently.

[NP-19] PIBM2024-0731-14

Software for high-throughput data acquisition of macaques whole brain imaging system

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Abstract: Optical microscopic imaging system is a powerful tool for studying the complete brain structure and function of non-human primates such as macaques. However, the data flux of 4 GB/s of this system and the continuous data acquisition of more than 500 hours place high demands on the data transmission capability of the software. This paper proposes a multi-memory producer-consumer strategy where the image acquisition and image compression run in parallel. The strategy removes the strong coupling between image acquisition and image compression, reducing the total amount of data, and improving the data transmission speed. The effect of the strategy is calculated theoretically and tested in practice. The result concludes that the scheme has important practical significance for the image acquisition of macaque brain biological samples. Furthermore, the function of automatically adjusting the region of interest is added, which greatly reduces the

acquisition time and the total amount of data. Finally, this paper realizes a high-throughput automated imaging software with image acquisition and storage functions.

[NP-20] PIBM2024-0731-15

A high-resolution, large-scale, 3D platform for imaging whole-bodies of mice

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Abstract: The whole-body imaging of mice is limited by factors such as sample transparency, long sample processing and imaging time, and imaging platform structure. We have developed a whole-body fMOST system based on fluorescence tomography, which does not require transparent processing of the sample and has an efficient sample cutting method that can obtain high-resolution images of the entire mouse body in the shortest time. During imaging，we can simultaneously obtain PI staining images and transgenic fluorescent labeling images of the same sample, with a voxel resolution of 0.54 μm * 0.54 μm * 3 μm, achieving the highest imaging resolution for whole body imaging of mice. Using the whole-body fMOST system，we visualized the distribution of nerves, blood vessels, and tumors throughout the body of adult mice, and observed these specific structures and their interactions with surrounding cells by dual-channel imaging. In addition, for the whole-body vascular images, we have developed a deep learning based framework for quantifying and analyzing the vascular systems of different tissues obtained from the whole-body fMOST system. We used a network structure based on Full-Resolution UNET and attention gates to segment blood vessels, achieving human level accuracy. This method can quantitatively analyze the vascular structure of different tissues throughout the body. For example, statistical analysis of the morphology of bone transparent cortical blood vessels shows that they are significantly larger in size compared to ordinary bone blood vessels, which corresponds to their function of transporting immune cells. This method can be used to quantify the morphology of blood vessels in different tissues.

[NP-21] PIBM2024-0731-22

Registration of Mesoscopic Whole-Body Imaging Data in Mouse

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Abstract: Submicron-resolution mesoscopic whole-body data in mouse enables systematic study of the entire physiological structures at the single-cell level, including neuronal projections, vasculature, tumors, and more. To compare and analyze structural and functional differences between individual mouse, it is essential to register imaging data to a reference standard body position. However, the complexity and variability of individual mouse structures become more pronounced at high-resolution imaging, where the rich voxel information provided by optical imaging reduces the tolerance for registration errors and significantly increases data volume. Consequently, existing methods struggle to balance accuracy and efficiency, making it difficult to compute accurate deformation fields within a limited timeframe. Here, we proposes an anatomical principle-based technique for whole-body data registration in mouse. The technique uses mouse skeletal structures as reference points and combines local linear and nonlinear deformation models to achieve accurate and efficient image registration. Additionally, we demonstrate that this method maintains topological consistency before and after registration without introducing anatomically incorrect deformations. We believe this technique can significantly improve the consistency and usability of mesoscopic optical imaging data of the whole mouse body, thereby advancing research in areas such as the mouse nervous system, vasculature, and skeletal structures.

[NP-22] PIBM2024-0731-23

Ultrafast 3D segmentation network for 3D neuronal volume

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Abstract: Brain-wide 3D optical neuronal image at high resolution has enabled individual neuron reconstruction and initiated new strategies for neural circuit analysis. Fast and precise segmentation is essential in neuronal volume processing, especially for whole-brain data contained over terabyte-voxels. Here we present an ultrafast 3D network, simplified deep-Layer aggregation supervision network (SDASN), for complex neuronal morphology segmentation. SDASN facilitates strong integration of multiscale feature maps by deep aggregation and full supervised mechanism to improve low signal noise ratio image prediction. A sparse data stitching and storage (SDSS) strategy is applied to further shorten the 3D processing time and reduce the storage capacity of predicted result. The proposed SDASN achieved nearly the fastest 3D inference speed of the current reports with SDSS. It only took about 0.4 second on a 300×300×300 volume, which was about 150 times of the typical 3D UNet, and also saved about 319 times of storage capacity of predicted result compared with normal storage method. It outperformed present simple network and reached similar performance of manual annotation and 3D UNet on neuron segmentation. A TB-sized whole-brain neuron

image could be segmented using SDASN quickly, further promoting neuron tracing and analysis.

[NP-23] PIBM2024-0731-28

3D optical imaging of cleared intact organs with consistently high quality integrated with vibration tissue sectioning

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Abstract: Combining tissue clearing with optical microscopy is a commonly used method for three-dimensional imaging of intact organs at single-cell resolution. However, the clearing reagents usually struggle to penetrate uniformly and deeply for large-volume tissue. As imaging depth increases, the unavoidable light absorption and scattering effects within the tissue lead to degraded imaging quality. Moreover, long working distance objectives are typically chosen to cover centimeter-scale samples, but their lower numerical apertures limit imaging resolution. To address these issues, this study developed a novel acquiring method for intact cleared organs with three-dimensional consistently high resolution and high efficiency, i.e., introducing vibration sectioning into cleared tissue imaging. We evaluated the sectioning and transparency performance of tissues after different clearing treatments. Next, we optimized steps including decolorization and delipidation, structural labeling, refractive index matching, and tissue embedding, developing a clearing method that is compatible with high-precision cutting. We established a new technical route for imaging acquisition of intact organs integrating the developed method with fluorescence micro-optical sectioning tomography (fMOST). To ensure uniformly high imaging quality over the whole organs, the sectioning thickness was set at 80-100 μm. The total acquisition time was reduced by about 30% compared with the tissue imaging without clearing due to less tissue cutting required. The whole organ images with a voxel resolution of 0.32 × 0.32 × 1 μm^3 of the mouse brain, heart, kidney, liver, spleen, and tongue were acquired. Notably, structures like heart valves and tongue taste buds demonstrated the advantages of this technique in studying delicate suspended structures. The technical solution developed in this study provides a novel approach for the rapid and high-quality acquisition of fine structures within intact organs.

[NP-24] PIBM2024-0731-31

An intact brain RNA fixation method compatible with preserving fluorescence and morphology

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Abstract: Spatial transcriptome (ST) has rapidly developed in the past few years, which provides a technical basis for studying the spatial heterogeneity in the tissue and the spatial organization of neural circuits. However, sample preparations for ST limit the simultaneous acquisition of accurate spatial information and high-quality transcriptomic information. Exclusive dependence on fresh starting material for sample preparation makes them difficult to meet the needs of long-term experiments; Fixation and segmentation for tissue often reduce the accuracy of spatial information and the integrity of single-cell RNA. In this study, we developed a novel RNA fixative, thereby establishing an intact brain RNA fixation method for spatial transcriptome that is compatible with preserving intact brain morphology, RNA integrity and neuronal fluorescence. This method achieved long-term preservation for morphology and in situ RNA at room temperature, increasing the time of samples processing and subsequent experiments. It also effectively reduced tissue deformation, RNA degradation and loss of fluorescence, ensuring the acquisition rate of accurate spatial information and high-quality RNA in single cell. The barrel cortex is one of the classical models to study the structure and integration function of the cortical column. The cells of barrel and septum have a precise spatial organization in the fourth layer (L4). By using the combination of virus tracing, DAPI staining and Patch-seq, we established the spatial localization model and acquisition scheme for single L4 cell in barrel cortex treated with the RNA fixative. Further, RNA-seq data indicated that the transcriptomic subtyping and gene expression patterns were related to the sublayer along dorsoventral axis and the spatial organization of the barrel-septa in L4. These results confirmed this method can be effectively applied to the study of single-cell transcriptomes and spatial transcriptomes at room temperature, and will provide support for studies on brain spatial informatics.

[NP-25] PIBM2024-0731-33

Ultra-thin vibration cutting and three-dimensional high-resolution imaging of the whole heart

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Abstract: Three-dimensional visualization of cardiovascular and cardiomyocytes at the single-cell resolution will aid in understanding the heart's structure and function. However, existing vibration cutting is unable to achieve continuous cutting of heart tissue less than 10 μm due to the high elasticity and rich cavity structure of the heart tissue. This has hampered the application of existing whole-organ imaging technologies that combine thin tissue cutting and precision optical imaging, such as fluorescence micro-optical sectioning tomography (fMOST), to cardiac tissue. To address this issue, a novel vibratome with a frequency of 180 Hz and a suppressed motion error of less than 1 μm has been developed, and the high-frequency vibration can

cause local stiffness enhancement in elastic tissue, enabling cutting of heart tissues with low surface smoothness. Further, we developed a vacuum-assisted sample preparation technique that allows agarose to fill cardiac cavities that cannot be covered by natural immersion. The highly agar-filled heart tissue can better resist deformation during the cutting process. We successfully prepared a heart sample with a filling rate of 94% and achieved 5 μm heart tissue cutting. Combining these new methods with fMOST, a complete heart was imaged at a voxel resolution of 0.32 × 0.32 × 1 μm^3. Results demonstrated well-preserved suspended structures and cavities within the heart. Elastic myocardial structures were smoothly cut, and the periodic sarcomere structures on myocardial cells were discernible. Based on high-quality imaging results, structures such as valves, tendons, and vessels can be reconstructed in three dimensions. The developed technologies in this study are useful for mapping the detailed structures of the whole heart, providing a valuable tool for studying the mechanisms of heart diseases and drug development.

[NP-26] PIBM2024-0731-42

Computational adaptive optical microscopy for high-resolution large-FOV bioimaging

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Abstract: High-resolution investigations across a large field of view (FOV) are essential for a thorough understanding of biological structures and functions. However, this is challenging due to optical aberrations induced by sample heterogeneity, especially for bioimaging across large-FOV. Adaptive optics (AO) technologies, which actively measure and correct aberrations, have been commonly applied for bioimaging. Despite their effectiveness, AO typically relies on specialized wavefront sensing and corrective devices, resulting in a small effective FOV. Consequently, multiple AO operations are often required for large-FOV imaging of optically complex samples, increasing system complexity and experiment time.

Computational AO approaches have recently emerged to reduce hardware requirements. However, these methods usually require large external datasets for training and still necessitate hardware for wavefront correction. A recently developed computational AO method can measure and correct aberrations in a purely computational manner, but its applicability for large-FOV imaging is constrained by the diffraction-limited sampling requirement. In this study, we propose a coordinate-based neural network inspired by physical models of optical microscopes for aberration estimation and correction without the need for diffraction-limited sampling. We validated our approach across multiple imaging modalities, including conventional widefield microscopy, widefield microendoscopy, two-photon microscopy, and super-resolution structured illumination microscopy. Our results show that our technique is capable of correcting aberrations across large FOVs, demonstrating our approach as a general solution for high-resolution, large-FOV bioimaging.

[NP-27] PIBM2024-0802-2

Adaptive Closed-loop Two-photon Holographic Optogenetic Stimulation

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Abstract: Two-photon optogenetics enables precise manipulation of neural activity with cellular resolution and millisecond precision in three dimensions, opening up possibilities for all-optical studies of the structure and function of neural circuits. However, achieving long-term closed-loop studies of neural ensemble activity remains challenging due to insufficient excitaion of neurons and increased phototoxicity from excessive stimulation. Here, we propose an adaptive closed-loop two-photon holographic optogenetic method that can precisely regulates laser excitation among a group of neurons based on their calcium response. This is achieved using an enhanced weighted Gerchberg-Saxton (EWGS) algorithm, which excels in target point power ratio (from ~0.8 to ~0.95) and excitation uniformity (from ~75% to ~95%), while significantly increasing iteration speed by approximately three-fold. Through this iterative process, the total laser power used for holographic stimulation of ~30 neurons is reduced to less than 65% of the original. This improvement allows for more precise and effective stimulation of neural ensemble with less photodamage, facilitating long-term closed-loop neuroscience studies.

[NP-28] PIBM2024-0804-1

Photo-stimulation of meningeal lymphangiogenesis for therapy of traumatic brain injury

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Abstract: Traumatic brain injury (TBI) is often accompanied by an increased intracranial pressure (ICP), which aggravates recovery processes in the post-TBI period. It was recently discovered that TBI is accompanied by a loss of meningeal lymphatics (MLVs) playing an important role in brain's drainage (BD). Therefore, the

development of technologies for augmentation of functions of MLVs is very important in a progress of effective therapy of TBI. Here we present the new technology of photobiomodulation (PBM, LED-1050 nm, 30 J/cm^2, pulse mode) of meningeal lymphangiogenesis in C57BL/6 male mice as a new technology for therapy of TBI. Using an immunohistochemistry and confocal imaging, we confirmed that TBI was accompanied a significant reduce of MLVs. These changes were associated with an increase in ICP and a suppression of BD (it was evaluated by an assessment of lymphatic removal of contract agent from the brain). A 10 day-course of PBM (3 days after TBI) caused an increase of MLV coverage that restored BD and reduced ICP. PBM improved neorological outcomes and metabolism (the test with the Phenomaster TSE). It was found that PBM increases the formation of nitric oxide and singlet oxygen in the isolated MLVs that are regulating factors of lymphatic contractility.

Thus, these results demonstrate that PBM is a promising tool for therapy of TBI by stimulation of meningeal lymphangiogenesis that contributes improvement of neurological outcomes and metabolism.

This study was supported by grant from Russian Science Foundation No. 24-45-00010.

[NP-29] PIBM2024-0810-2

Rapid labeling of molecular types of neurons based on CRISPR/Cas9 homology-independent targeted integration

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Abstract: Labeling neuronal molecular types assists us in characterizing the morphological, functional, and other attributes of neuronal cell types, which is a crucial aspect of unraveling the workings of the brain. There are considerable difficulties to rapidly and precisely accomplish this objective. To overcome this, we have developed a method based on HITI (CRISPR-Cas9 homology-independent targeted integration) gene insertion, which enables the co-driven expression of reporter genes and endogenous genes. We have termed this approach CRISPR-Mapping. To achieve specific and efficient labeling of neuronal molecular types, we assessed the effects of wtCas9, HiFiCas9, and SuperFiCas9 mutants and selected HiFiCas9 for its low off-target rate and minimal toxicity. Employing the HiFiCas9-based CRISPR-Mapping technique, we have successfully labeled various cell types and applied it to studies on calcium signaling recording, electrophysiology, projection, and neuronal circuit connectivity. The results indicate that this labeling strategy, which integrates AAV viruses with CRISPR/Cas9, facilitates rapid and effective neuronal labeling. It allows for the high-intensity labeling of neuronal molecular types in wild-type mice, reduces reliance on transgenic mice, and achieves labeling accuracy exceeding 80%. Furthermore, this method exhibits broad applicability. This technology expands the application spectrum of our method and existing viral labeling tools, enhancing the array of options available to researchers.

[NP-30] PIBM2024-0814-1

Study on brain function characteristics of children with cerebral palsy during walking based on fNIRS

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Abstract: Background Motor dysfunctions in children with cerebral palsy (CP) are caused by brain damage. Understanding the functional characteristics of the brain is important for rehabilitation. **Method** The differences of brain function characteristics between 17 CP children and 13 children with typical development (CTD) during walking were compared. Firstly, the average amplitude of HbO_2 signals at 0.01-0.1HZ was calculated using wavelet transform to characterize the hemodynamic activation response. Then, the wavelet coherence at different scales in this frequency band was calculated as an index to reflect functional connectivity. Based on this, the connectivity between different brain regions were analyzed and the network topological characteristics were calculated. Finally, the normalized phase transfer entropy between channels were calculated using the method of phase flipping and phase space division to evaluate the directional information flow direction, and the phase transfer entropy was taken as the edge of the network to analyze the directed weighted network. **Results** Compared with CTD, only the prefrontal lobe of non-dominant side was significantly activated in CP children, the connectivity between the motor area of non-dominant side and the ipsilateral prefrontal and contralateral motor areas were decreased, the clustering coefficient of the brain network was decreased and the global efficiency was increased, the channel output and average information outflow intensity of the prefrontal lobe in the non-dominant side and the motor area in the dominant side were all increased. **Conclusion** CP children showed significant differences on brain activation and network connectivity compared with CTD during walking, and the different information flow pattern may be a compensatory mechanism for the impaired brain function of CP children. This study provided effective indexes for evaluating the real-time effects of exercise training on brain networks.

[NP-31] PIBM2024-0814-2

PointTree: automatic and accurate reconstruction of long-range axonal projections of single-neuron

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Abstract: Single-neuron axonal projections reveal the route map of neuron output and provide a key cue for understanding how information flows across the brain. Reconstruction of single-neuron axonal projections requires intensive manual operations in ten terabytes of brain imaging data, and is highly time-consuming and labor-intensive. This dilemma stems from the following irreconcilable contradiction. The snowballing effect of a single reconstruction error requires highly accurate reconstruction algorithms. However, almost all algorithms focus on skeleton extraction from images or signal-enhanced images and fail to overcome the interference of densely distributed axons. To address this issue, we revolutionize the current reconstruction framework by constructing a point assignment-based method. Our method generates a series of cylindrical point sets representing the axonal shape and constructs connections between skeleton points, the centers of the point sets, using cylindrical morphology, which in principle nicely separates densely distributed axons. Moreover, we design a minimal information tree model to suppress the snowball effect of reconstruction errors. Our method successfully reconstructs single-neuron axonal projections across hundreds of GBs images with an average of 80% F1-score, while current methods only provide less than 40% F1-score reconstructions from a few hundred MBs images. This huge improvement is helpful for high-throughput mapping of neuron projections.

[NP-32] PIBM2024-0819-3

Estimate the 3D fiber orientation distributions of white matter in the mouse brain by integrating mesoscopic nissl-staining with dMRI data

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Abstract: Diffusion magnetic resonance imaging (dMRI) is currently the only non-invasive tool for indirectly estimating the white matter fiber structure based on the diffusion characteristics of water molecules. However, current dMRI-based fiber tract reconstruction methods predominantly focus on the macroscopic scale, which limits their ability to accurately capture the structural details of white matter fibers at the cellular resolution level.

With the continuous advancements in mesoscopic imaging techniques, white matter fiber reconstruction based on mesoscopic brain imaging provides an important reference for the mesoscopic mechanisms underlying dMRI. In this study, isotropic Nissl-stained fMOST imaging data of the mouse brain were collected to estimate the whole-brain white matter fiber orientation distribution. This estimation was derived from the glial cell distribution patterns within white matter regions and subsequently compared with dMRI data from the corresponding spatial domain. Additionally, a deep learning network was demonstrated, which, when trained with fiber orientation distributions (FODs) derived from Nissl-stained image, can guide the estimation of FODs from dMRI data. This study shows how the distribution of glial cells at the mesoscopic scale can guide dMRI-based fiber tractography. Compared to constrained spherical deconvolution, the reconstruction results of the method proposed in this study showed an improvement of approximately 0.15 in the angular correlation coefficient. Importantly, the translation from high-resolution mesoscopic images to macroscopic fiber tracts allows for a more detailed understanding of brain structure, which can be applied to precise research on certain brain diseases.

[NP-33] PIBM2024-0819-6

Enhancement of Working Memory in Individuals with Mild Cognitive Impairment through Simultaneous Transcranial Magnetic Stimulation and Transcranial Photobiomodulation

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Abstract: This study investigates the effects of dual non-invasive brain stimulation techniques—transcranial Photobiomodulation (tPBM) at 1064 nm and high-frequency transcranial magnetic stimulation (TMS)—on enhancing working memory in individuals with mild cognitive impairment (MCI). A total of 88 participants were randomly assigned into four groups (22 participants each): dual sham stimulation, tPBM combined with TMS, single tPBM, and single TMS. The experimental design involved several steps: 1) resting-state near-infrared spectroscopy (NIRS) measurements to assess baseline brain activation, 2) cognitive task performance to obtain initial cognitive scores and task-state NIRS data reflecting brain activation levels, 3) application of the neurostimulation interventions, and 4) post-stimulation cognitive task performance to acquire follow-up cognitive scores and task-state NIRS data. By comparing the improvements in cognitive task scores with NIRS indicators of brain activation and functional connectivity during task performance, we aim to validate our hypothesis that both TMS and tPBM can enhance cognitive abilities (specifically working memory), with the combined application yielding superior results. The findings suggest that dual stimulation not only improves working memory performance but also enhances task-related brain activation and connectivity, indicating a

synergistic effect. This study highlights the feasibility and safety of using these non-invasive neuromodulation techniques in concert as an effective intervention for cognitive enhancement in the MCI population.

[NP-34] PIBM2024-0819-17

Mapping the density distribution pattern of microvasculature in whole-mouse brain

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Abstract: Analyzing the vascular network structure of the brain is crucial for understanding brain function and for the prevention and treatment of cerebrovascular diseases. By studying indicators such as the length density and branching point density of the brain's microvascular network, we can gain a better understanding of the brain's vascular network and provide a scientific basis for cerebrovascular disease research. Traditional methods rely on statistical analysis of isolated brain regions, which fail to capture the spatial distribution characteristics of micro-vessels across the entire brain and overlook spatial information from different brain regions. To address this, we propose a computational pipeline for the spatial distribution of vascular density in the brain. First, we use a deep learning model to segment brain vascular images from fMOST imaging of mouse brains. Then, we perform skeletonization on the 3D vascular segmentation images and obtain vessel diameter information through distance transformation. Finally, we filter capillaries based on their diameter and calculate the feature parameters of these capillaries to acquire vascular parameter distributions across the entire brain. The entire process is enhanced by MPI parallel processing and multithreading techniques to improve image processing efficiency. Results indicate that our proposed method can capture the spatial distribution characteristics of microvascular density across the whole brain by integrating multiple datasets. Additionally, we calculated the brain vascular density in normal mice and Alzheimer's disease (AD) mice to verify the differences in vascular distribution between the two groups. This method provides a powerful tool for comprehensive research on brain vasculature.

[NP-35] PIBM2024-0819-24

3D X-Ray reconstruction of neuronal microstructure networks in mouse pbrain hemisphere

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Abstract: Understanding the structure and function of the brain remains one of the most challenging scientific frontiers in the world. The study of brain microstructure networks is crucial as it provides essential insights for the analysis of brain functional imaging data. In this study, we aimed to visualize the microstructure networks within a mouse brain hemisphere, encompassing axonal tracts and vascular networks. We gathered hard X-ray datasets and established an automated pipeline for segmenting axons and the vascular network within volumetric images.

Synchrotron radiation hard X-ray (SRX) phase contrast tomography offers fully quantitative 3D data that ultimately attains a higher spatial resolution and a larger field of view (FOV) concurrently. We employed a comprehensive approach involving sample preparation, SRX phase contrast tomography, and 3D image analysis to extract neuronal information. The whole mouse brain hemisphere (Figure 1), vessel networks (Figure 2), and axonal tracts network (Figure 3) are depicted as shown.

Our work focused on reconstructing and analyzing these microstructure networks within the mouse brain hemisphere. We harnessed deep learning algorithms to automatically identify and reconstruct axonal tracts, vessels, and neurons from the hard X-ray datasets. Our statistical analysis of various neuronal microstructures was grounded in 3D reconstruction, which offers greater accuracy than measurements based on two-dimensional images. The workflow we developed for reconstruction and analysis can also be applied to study neuronal microstructures in other models or disease contexts.

At the whole brain scale, we visualized the mouse brain hemisphere; And at the local fine scale, the coarse-grained structures such as axonal tracts, blood vessels, and neurons were reconstructed. Hundreds of axonal branches seemed to form the “bus” of signal transmission between brain regions. The distance between blood vessels and neurons in a brain region was uneven. The analytical results provided a structural basis for understanding the brain.

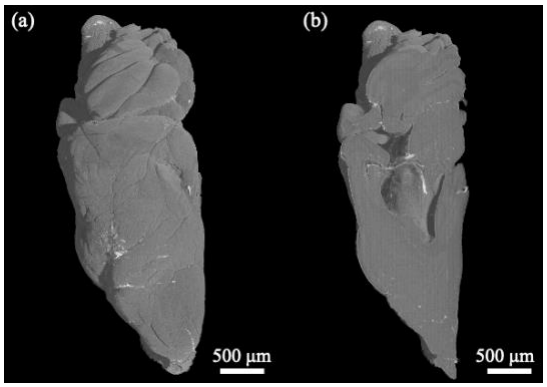

Figure1. Three-dimensional visualization of hemisphere of murine brain. (a) Side and (b) cutaway views of the entire hemisphere. Scale bars:500 μm

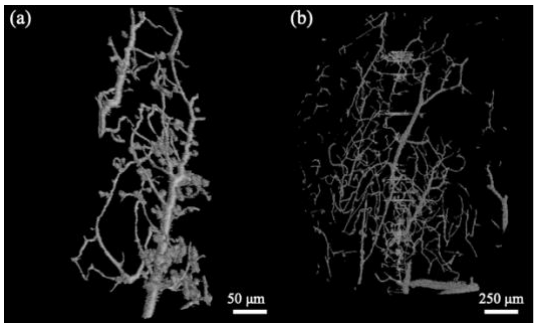

Figure 2. Three-dimensional rendering of vessels of murine brain. (a)parts and (b) whole views of vessels of the entire hemisphere. Scale bars: 50 μm and 250 μm

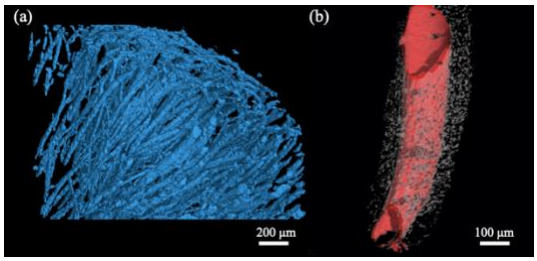

Figure 3. visualization of microstructure of murine brain. (a)Axonal tracts. Scale bars:200 μm. (b) neurons and a part of vessel of the entire hemisphere. Scale bars:100 μm

[NP-36] PIBM2024-0820-10

Simultaneous two-photon and three-photon microscopy for multi-ROI and multi-depth brain imaging

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Abstract: Multiphoton microscopy has become an essential tool for visualizing neurobiological phenomena. While two-photon imaging is restricted to the cortical regions of the brain, three-photon imaging can penetrate subcortical areas in mouse models. The integration of two-photon and three-photon imaging holds significant promise for advancing neuroscience research by enabling deep imaging in the neocortex and the subcortical region simultaneously. However, a major challenge remains in the simultaneous acquisition and differentiation of their signals excited by ultrafast laser pulses. Currently, synchronization methods for two-photon and three-photon imaging mainly use spatiotemporal multiplexing or spectral separation techniques. Spatiotemporal multiplexing requires extensive system modifications, increasing complexity, while spectral separation relies on the spectral properties of fluorescent proteins, which prevents the synchronized acquisition of the same type of fluorescent protein. This presentation introduces a synchronous acquisition method that leverages the difference of repetition rate between pulsed lasers using in two-photon and three-photon imaging. By using the trigger signal from the three-photon laser for synchronization and applying phase shifting and frequency doubling to control the two-photon laser and signal acquisition module, this method enables simultaneous two-photon and three-photon imaging for multi-ROI and multi-depth brain imaging.

[NP-37] PIBM2024-0820-15

Treatment of peripheral nerve injury with platelet-rich plasma based on multimodal imaging

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Abstract: Peripheral nerve injury is one of the most common causes of permanent disability in motor and sensory functions. Platelet-rich plasma (PRP) contains a variety of bioactive factors, which can promote the synthesis of new connective tissue and vascular remodeling, so as to assist the recovery of damaged nerve tissue and have a positive effect on nerve tissue regeneration. However, little is known about the specific blood supply requirements that PRP promotes during peripheral nerve repair and how these requirements relate to their function. In particular, it is unclear to what extent the blood supply requirements during peripheral nerve regeneration are related to their conduction function, and to what extent they are related to the viability of nerve tissue. Therefore, we put forward this scientific question: what is the influence of blood supply on the peripheral nerves and the vascular structure and hemodynamics of the lower limbs during the repair of peripheral nerve injury. Here, we established a model of peripheral nerve injury in SD rats, treated with PRP, and then observed the repair process of sciatic nerve injury by PRP through imaging combined with histological and serological detection methods. Furthermore, our study reveals that in the process of PRP repair of sciatic nerve, the results of multimodal imaging showed that the structure and hemodynamics of sciatic nerve and lower limb blood vessels would change accordingly, which was similar to the results of behavior and histology. In summary, this analysis could help provide new detection methods and preclinical research evidence for the treatment of peripheral nerve injury.

[NP-38] PIBM2024-0821-1

A large-volume three-dimensional tissue architectonic mapping method for intact organs at high resolution

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Abstract: Architectonic imaging and studying of different tissues and animal species at the mesoscopic and 3D level is important for our understanding of organ compartments, diseases and working mechanisms. However, traditional histology researches were conducted mainly on either tissue slice or at low resolution, technically limited by both staining and imaging. Here, we proposed a large-volume, high-resolution architectonic imaging method based on surface fluorescence sectioning microscopy (SFST) and ultrathin

staining on resin embedded samples. This method dispensed with the necessity of tissue pre-staining and is unhampered by specimen size, animal species, or developmental limitations. Resin-embedded specimens were stained on the submicron scale with serial sectioning to achieve high staining uniformity and high axial resolution of tomography. Architectonic probes enabled distinct fluorescent intensities and textural features to be exhibited by different cellular compartments, contributing to a clear and differentiated visualization of tissue architecture. Moreover, the combination of two probes revealed more architectonic information and allows superior visualization of structures such as blood vessels, surpassing the capabilities of single-probe staining. To characterize the performance and examine the robustness of this pipeline, we imaged and reconstructed the brain and other organs in C57 mice, along with the 3D structure of their internal components, such as cytoarchitecture, vessel network, muscle fibers, and nerve tracts. Furthermore, it had proven its potential in other model animals, as evidenced by the successful visualization of the macaque's prefrontal cortex. Our method can easily capture a variety of whole-organ tissue architectures for three-dimensional, multi-color, high-contrast at the mesoscopic-scale, potentially making it useful for applications in 3D histopathology.

[NP-39] PIBM2024-0828-2

Characterization of cerebrovascular changes in Alzheimer's disease mice by photoacoustic imaging

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Abstract: The cerebral vasculature plays a significant role in the development of Alzheimer's disease (AD), however, the specific association between them remains unclear. In this paper, based on the benefits of photoacoustic imaging (PAI), including label-free, high-resolution, in vivo imaging of vessels, we investigated the structural changes of cerebral vascular in wild-type (WT) mice and AD mice at different ages, analyzed the characteristics of the vascular in different brain regions. The results showed that vascular density and vascular branching index in the cortical and frontal regions of both WT and AD mice decreased with age. Meanwhile, vascular lacunarity increased with age, and the changes in vascular structure were more pronounced in AD mice. Here, we utilized *in vivo* PAI to analyze the changes in vascular structure during the progression of AD, which will provide more intuitive data for the study of the correlation between cerebrovascular and the development of AD.

[NP-40] PIBM2024-1016-4

Automatic brain tumor identification using label-free nonlinear optical microscopy and deep learning

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Abstract: Surgical resection is the primary treatment for brain cancer, where maximizing cancer removal while preserving adjacent healthy tissue is crucial. This task is challenging due to the invasive nature of brain tumors. Current intraoperative histopathology methods, such as frozen section and smear preparation, have drawbacks like labeling requirements and being time-consuming and labor-intensive. In this paper, we propose an automatic, label-free method for brain tumor identification using nonlinear optical microscopy (NOM) combined with deep learning. NOM is employed to capture dual-modal images of brain tissue, including two-photon excitation fluorescence (TPEF) and fluorescence lifetime imaging (FLIM) images. These images serve as input for a U-net network, which accurately identifies tumor regions. This method was tested on tumor-bearing nude mice. Results show that NOM can reveal cerebral structures and metabolic conditions. By extracting structural features and microenvironment information from NOM images, U-net could distinguish between tumor and peritumor regions with an accuracy of 0.9. The deep learning-based, label-free NOM approach promises automatic identification of cancerous versus non-cancerous tissues and is expected to integrate with endoscopy and fiberscopes, offering a promising tool for characterizing cancer and cerebral structures during brain surgery.

Translational Biophotonics

[TP-1] PIBM2024-0727-1

High-speed k-linear swept laser using acousto-optic deflectors with Doppler shift compensation for optical coherence tomography

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Abstract: Swept laser based on the acousto-optic deflector (AOD) is a promising swept source in optical coherence tomography (OCT) applications for its high wavenumber linear sweep without mechanical motion. However, the poor coherence length and the elongated cavity of the laser imposed limitations on the acquisition of high-quality images with adequate imaging depth and high imaging speed. In this letter, we demonstrate a compact high-speed wavenumber linear swept laser based on AOD using Doppler shift compensation, achieving a high linearity of Pearson's R of 0.999991, a duty cycle of ~100%, an extended coherence length of 5.7 mm, an output power of 18 mW and excellent phase stability at a sweep rate of 500 kHz. OCT structural images with a system sensitivity of 103.2 dB and OCT angiography (OCTA) of human palm in vivo have been successfully performed, serving as a compelling demonstration of the excellent performance of this swept laser. We believe that the proposed laser will be of high potential in various clinical and industrial applications in the future.

[TP-2] PIBM2024-0727-5

Optical biomarker of metabolism for breast tumor diagnosis: Insights from subcellular dynamics

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Abstract: The diagnosis and grading of tumors rely on histopathological examinations, and aberrant cellular metabolism has long been recognized as a primary feature of cancer. Therefore, imaging modalities providing rapid, high-quality histology with metabolic contrast would be highly appealing. Interference offers a highly sensitive mechanism for capturing the metabolic dynamics of the subcellular scatterers. Here, we demonstrate active phase modulation-assisted dynamic full-field optical coherence tomography (APMD-FFOCT), which, for the first time to our knowledge, can clearly quantify metabolic dynamics through a label-free imaging technique. This novel technique enables imaging and dynamic analysis of subcellular structures such as the nucleolus and chromatin, tracking their changes throughout the apoptotic process in tumor tissues. Therefore, it can further supply fast and label-free histology within seconds, much faster than standard histological techniques. Furthermore, by analyzing APMD-FFOCT images of 21 independent samples across various breast tumor grades, we demonstrate that the dynamic intensity ratio of nucleus to cytoplasm correlates dramatically with tumor malignancy, which is expected to optically provide a new biomarker for breast tumor grading.

[TP-3] PIBM2024-0731-40

Research on multi-focus parallel scanning system for femtosecond laser corneal refractive surgery

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Abstract: Myopia is a public health issue that cannot be ignored. SMILE (Small Incision Lenticule Extraction) refractive surgery is a new-generation laser treatment for myopia, widely promoted for its minimally invasive and safety. Since its successful clinical application, the surgical equipment for SMILE has undergone continuous technological advancements, with laser scanning speed being one of the crucial performance enhancements. Increasing the scanning speed can improve the success rate and safety of the surgery while reducing the incidence of related complications. However, current commercial surgical systems employ single-focus scanning modes, with their scanning speed limited by the scanners, nearing a bottleneck. To surpass this bottleneck, multi-focus parallel scanning is a promising strategy. Although this concept has been proposed for some time, there have been no related products or experimental results reported to date. Our team has developed a prototype system for multi-focus parallel scanning in femtosecond laser corneal refractive surgery and has demonstrated a multi-focus parallel scanning SMILE surgery on ex vivo pig eyes for the first time. The laser scanning for the SMILE surgery was completed in 8 seconds, compared to the 23 seconds required by commercial systems with the same device parameters, achieving more than twice the scanning speed. This work will also continue to advance towards clinical translation, assisting in the implementation of national eye health plan.

[TP-4] PIBM2024-0731-43

Enhancing cervical cell screening with CytoGPT: a multimodal large model integrating expert knowledge for improved accuracy and Interpretability

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Abstract: Cervical cell screening is a critical preventive measure in reducing the incidence and mortality of cervical cancer. Recent advancements in multimodal large models present a significant opportunity to enhance the quality and efficacy of this screening process. In this study, we present CytoGPT, a model that integrates the knowledge of pathology experts by effectively incorporating multimodal information, including visual data from cytological images and textual data from clinical reports. We have built a dataset of 200,000 image-text pairs to align the vision encoder with a large language model (LLama3.1-8b) for the first pre-training stage. Additionally, we developed a 50,000-instruction dataset for the second stage of fine-tuning. The performance of CytoGPT was evaluated on both public and private datasets, demonstrating superior accuracy and interpretability compared to MiniGPT-4 and human pathology experts. Our findings indicate that CytoGPT not only enhances the accuracy of automated screening but also provides clear, interpretable insights into the decision-making process. This work underscores the potential of leveraging multimodal large models to push the boundaries of cervical cancer prevention strategies, ultimately leading to better patient outcomes and more effective screening processes.

[TP-5] PIBM2024-0731-46

Visualization of Hydrogen Polysulfides Level in Type 2 Diabetes via a Mitochondria-Targeted Near-Infrared Fluorescent Probe

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Abstract: Endogenous hydrogen polysulfides (H2Sn, n>1) was suggested to be critical regulators in redox biology. H2Sn can regulate tumor suppressor activity, inhibit glucose-stimulated insulin secretion, and so on. However, their exact action mechanisms of are still poorly understood. A main reason is the lack of reliable detection methods for H2Sn. Herein we report a series of new H2Sn fluorescent probes based on H2Sn-mediated benzodithiolone formation. Among them, near-infrared fluorescence off-on Probe 6 with 2-((methoxycarbonyl)thio)benzoate as recognition unit showed high sensitivity and specificity to H2Sn. This probe was successfully applied in visualizing H2Sn in cells and mice in vivo. More importantly, the upregulation of H2Sn levels was also observed in type II diabetic mice. This study will provide an important imaging tool for understanding and exploring the progression of type II diabetes.

[TP-6] PIBM2024-0731-56

Is it possible to image the tissue surface directly through blood without removing the blood interference?

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Abstract: Blood often obscures the target tissue and impedes the surgical field during surgical procedures. To mitigate the interference caused by blood, hemostatic forceps and saline irrigation are commonly employed to expose the target tissue. However, these methods may increase surgical risk and cause certain damage to the patient. This study explores the possibility of imaging target tissues through blood using Monte Carlo simulations of photon transmission in a two-layer vascular model composed of a blood layer and a vessel wall. The Gaussian light source with the wavelength of 1270nm is employed, and the focal point of the incident light is precisely positioned at the interface between the blood layer and the vessel wall. The detector is located 3.5mm from the light source, and the outgoing light is collected by a fiber optic with a diameter of 1mm and an aperture of 0.3. The results reveal that as the depth of the blood increases, the intensity of the detected signal undergoes exponential decay, which demonstrates the correctness of our model. Compared with the incident light intensity, the light reflected from the interface is reduced by 10^{-4}~10^{-5}. With a higher incident power, the vessel wall below a 5mm-depth blood layer might be detected by a practical detector. This work may pioneer a new way for clinical diagnosis.

[TP-7] PIBM2024-0806-1

Enhanced OCTA Imaging through Conditional Guidance Diffusion for Artifact Removal

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Abstract: Optical Coherence Tomography Angiography (OCTA) is a revolutionary technology widely used in the diagnosis and management of fundus, skin and cardiovascular diseases. However, unavoidable movements, such as breathing, cause motion artifacts in images. Although recent advances in learning-based image inpainting methods for OCTA enface images have improved artifact removal, these methods still require the collection of large amounts of accurately labeled data and the generation of pseudo stripes to create paired training sets. Furthermore, the abundant structural information and flow intensity signals present in OCTA B-scans is nonnegligible. Hence, we proposed B-scan to Enface Conditional Diffusion Guidance (B2E-CDG) for translation from signal-void B-scan to correct B-scan. We introduce the normal B-scan in a connection manner and the specified reference B-scan in a gradient-based manner as style feature guidance into diffusion learning. Conditional guidance facilitates a more controlled and precise process for B-scan flow signal recovery. The requirement for labeled images collection and pseudo stripes is obviated, as the repetitive scanning nature of OCTA naturally results in paired datasets comprising signal-void and normal B-scans. The experimental results demonstrated that B2E-CDG effectively removes bold, low-transparency stripes and restores vascular and structual information obscured by artifacts, which fails in enface-based methods. This work shows superior vascular recovery and artifact removal capabilities in both metrics and downstream tasks, enhancing the usability of OCTA in diagnostics.

[TP-8] PIBM2024-0822-1

Wearable nanoplasmonic sensor based on surface-enhanced Raman scattering for multiplexed analysis of sweat

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Abstract: Wearable sweat sensors have evolved into essential tools for human health management, offering non-invasive sampling, efficient rapid detection, and real-time monitoring. They hold significant promise in delivering critical clinical insights into physiological diseases within the healthcare domain. Here, a flexible nanoplasmonic paper-based sensor based on surface-enhanced Raman scattering (SERS) was developed,

in which silver nanoparticles were loaded in the cellulose paper to enhance the Raman signals of targets via the generation of SERS “hot-spots”. Integrating micro sweat collection, transmission, and detection, this multifunctional chip combines a filter paper channel with a core-absorbing liquid phase. Noteworthy attributes of this paper-based sensor include softness, stretchability, and a non-irritating fit on human skin, offering a simple, quick, and cost-effective method for on-site sweat analysis. By circumventing the reliance on conventional bulky Raman detection instruments, this study adopts a handheld Raman spectrometer for seamless and swift quantitative analysis of various sweat components. The limits of detection for uric acid and glucose are 84 μM and 1 μM, respectively, with a pH range of 4-7.5,enabling wearable and in-situ optical sensing in the concentration range of sweat markers covering human physiology and pathology, and the detection time is only five minutes. This wearable biosensor would provide a new way for continuously monitoring the healthy status by collection and analysis of multiple component in human sweat, contributing to point-of-care testing (POCT) and personalized medicine applications.

[TP-9] PIBM2024-0919-1

AI-Assisted classification of lung adenocarcinoma subtypes using Swin-Transformer

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Abstract: Lung cancer, particularly lung adenocarcinoma, presents a significant challenge to global health and is a leading cause of cancer-related deaths. In this study, we focus on classifying various subtypes of lung adenocarcinoma, including lepidic, acinar, papillary, micropapillary, solid, mucinous, and cribriform, using deep learning techniques. We developed a model based on the Swin-Transformer architecture, which achieves impressive accuracy in subtype classification. We started by creating a well-annotated dataset of histopathological slides stained with hematoxylin and eosin (H&E), ensuring that our model was trained on data rich in essential tissue characteristics. We then trained the model to effectively differentiate between the subtypes. To enhance interpretability, we utilized Grad-CAM, a visualization technique that accurately locates tumor areas and helps identify subtle changes in the H&E images. Additionally, we employed RGB color filtering to assess the area proportions of different subtypes within heterogeneous tumor samples. This method allows for precise quantification of subtype distribution, which is crucial for understanding tumor behavior and guiding treatment decisions. By addressing the challenges posed by tumor heterogeneity, our work aims to improve diagnostic accuracy and potential treatment outcomes for patients. This research highlights the promising role of advanced imaging and deep learning in enhancing cancer diagnosis, ultimately leading to more personalized patient care. By integrating H&E image analysis, we hope to refine the accuracy of subtype classification and better support clinicians in making informed treatment choices.

[TP-10] PIBM2024-0726-3

Photoacoustic Fiberscope with Enhanced Imaging Speed for Gastrointestinal Endoscopy

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Abstract: Photoacoustic endoscopy offers a promising non-invasive imaging modality for gastrointestinal diseases by detecting laser-induced ultrasound waves. However, the development of flexible, compact photoacoustic endoscopes has been hindered by two main challenges: limited ultrasound detection sensitivity in confined spaces and restricted imaging speed due to rotational scanning methods. Building on our previous work in high-performance photoacoustic fiberscopes [*Nat. Commun*. 13, 7604 (2022), highlighted in *Optics in 2023* by Optica], we present a novel photoacoustic fiberscope with significantly enhanced detection sensitivity and imaging speed.

To address the first challenge, we developed an innovative fiber optic ultrasound sensor that simultaneously detects multiple vibrational modes (isotropic breathing and anisotropic compression) of the fiber. Utilizing a single-polarization, single-frequency laser as the acoustic sensing element, we measured the lasing frequency variation induced by these vibrational modes, by using an imbalanced Mach-Zehnder interferometer. This approach achieved an average noise-equivalent pressure density of 0.8 mPa/Hz$^{1/2}$ over an extended bandwidth of 6 to 37 MHz.

To improve imaging speed, we implemented a bundled fiber containing tens of thousands of cores for efficient guidance and scanning of pulsed light for photoacoustic excitation. This innovation increased the frame rate to 0.5 Hz, a significant improvement over conventional methods.

We conducted a longitudinal study of ulcerative colitis, repeatedly imaging the same inflammatory area over 14 days. Our results revealed inflammation-induced vascular congestion and increased oxygen saturation (sO2), followed by a recovery process. We also demonstrated the efficacy of our photoacoustic fiberscope by imaging multiple organs in a small animal model through a minimal abdominal incision.

The proposed photoacoustic fiberscope offers several advantages, including flexibility, miniaturization, and advanced imaging capabilities. Its potential applications extend to assessing hemodynamic and oxygenation functionalities across multiple organs, representing a significant advancement in gastrointestinal endoscopy and biomedical imaging.

[TP-11] PIBM2024-0726-4

Enhanced Gastrointestinal Endoscopy through Photoacoustic Tomographic Imaging with Optical Ultrasound Detection

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Abstract: Photoacoustic computed tomography (PACT) offers rich optical contrast and high resolution at significant depths, making PACT endoscopy a promising modality for gastrointestinal (GI) diagnostics and theranostics. However, traditional piezoelectric ultrasound sensors used in PACT face limitations due to the trade-off between sensor dimension, detection sensitivity, and angular coverage, resulting in shallow detection depths and incomplete vascular feature acquisition.

To address these challenges, we developed a novel gastrointestinal endoscope utilizing PACT with a fiber-optic ultrasound sensor. This sensor demonstrates superior performance compared to piezoelectric sensors, featuring broader bandwidth (center frequency: 60 MHz), higher sensitivity (noise equivalent pressure density, NEPD: 1 mPa/Hz$^{1/2}$), and full angular coverage.

In our endoscopic imaging setup, the sensor was scanned over an arc-shaped trajectory to capture photoacoustic waves generated through wide-field illumination. Rectal vessels were reconstructed by acoustic back projection. This configuration achieved endoscopic imaging with a 45 μm resolution and a penetration depth exceeding 7 mm, while providing a comprehensive angular spectrum of rectal vascular structures. Furthermore, by employing 532/1064-nm dual-wavelength illumination, the endoscope revealed intricate vascular structures at various orientations and oxygenation saturation levels within the swine rectum. The system successfully imaged vascular ranges with diameters from several tens to a few hundred micrometers across multiple layers, including the mucosal, submucosal, and muscle layers.

This technological advancement holds significant potential for enhancing the diagnosis and treatment of cancer and inflammatory diseases in the gastrointestinal tract, representing a promising step forward in GI endoscopic imaging.

[TP-12] PIBM2024-0729-6

Advanced Flow Dynamics Mapping Through Volumetric Photoacoustic Particle Velocimetry

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Abstract: Flow field analysis is crucial in biomedical applications such as drug delivery, dosage control, and hemodynamic studies. Current particle image velocimetry techniques face limitations in three-dimensional dynamic analysis in turbid media. This paper aims to achieve rapid three-dimensional flow field reconstruction and analysis using photoacoustic volumetric particle image velocimetry. Our developed photoacoustic imaging system provides rapid volumetric reconstruction without complex calibration, making it particularly advantageous for three-dimensional flow field analysis in deep tissues or turbid media. Additionally, photoacoustic volumetric particle image velocimetry excels in dynamic flow field analysis, offering real-time insights into fluid behavior. We used 20-50 μm nickel-coated polystyrene particles as tracers, uniformly added to the fluid. Particle images were captured at 20 ms intervals to calculate particle displacement over time, determining the flow field distribution, including velocity and vorticity fields. The particles were illuminated using a pulsed laser with a wavelength of 1064 nm, frequency of 50 Hz, and single pulse energy of 100 mJ, successfully analyzing the flow field in turbid milk. Additionally, we created flow fields in normal and obstructed

vascular phantoms using a circulation pump. The obstructed model simulated vessel narrowing due to lipid deposition on the vessel walls. Using non-transparent fluid to simulate blood flow, we observed changes in blood flow in both normal and narrowed vessels.

This study represents the first application of photoacoustic imaging in three-dimensional particle image velocimetry, achieving rapid and dynamic flow field analysis. Our findings demonstrate that photoacoustic volumetric particle image velocimetry provides excellent imaging performance in turbid media. The technique effectively addresses the shortcomings of traditional optical and ultrasound methods, offering a promising tool for flow field analysis in various biomedical applications.

[TP-13] PIBM2024-0730-34

Photoacoustic imaging of human peripheral microcirculation by using an omnidirectional optical ultrasound sensor

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Abstract: Effective imaging and monitoring of peripheral microcirculation are crucial for early detection of hemodynamic instability and organ dysfunction in intensive care and intraoperative settings. However, current bedside techniques often fail to detect microcirculatory impairments until significant organ damage has occurred. While photoacoustic imaging has emerged as a promising technique for assessing microvascular functionalities, its clinical adoption has been fundamentally constrained by bulky imaging probes and limited angular coverage.

To address these challenges, we have developed a miniaturized, omnidirectional optical ultrasound sensor that enables photoacoustic imaging of blood microcirculation in various monitoring sites across the human body, including fingers, palms, and arms. Our sensor incorporates a single-longitudinal-mode, single-polarization fiber laser that converts acoustic vibrations into laser phase variations. The optical signal is read out through self-delayed heterodyne technology, achieving significant amplification of optical phase variation. By detecting laser-induced ultrasonic waves using a single scan of the sensor, we can perform tomographic imaging to visualize fine structures of human subcutaneous blood vessels with a significantly enlarged detection angular coverage.

The sensor exhibits omnidirectional receiving capabilities, capturing complete angular spectrum information of microvascular structures. It achieves a spatial resolution of approximately 70 microns and an imaging depth of 7 millimeters. By employing multiwavelength excitation, the imaging system can extract microcirculatory hemodynamic and oxygenation function information.

The compact imaging is suitable for integration into bedside monitoring instruments in critical care settings. This technology offers a potential solution for preventing sepsis and other systemic microcirculatory dysfunctions, addressing the need for rapid, high-resolution imaging in clinical environments. Our approach paves the way for real-time, non-invasive monitoring of microcirculation, potentially revolutionizing patient care in critical settings.

[TP-14] PIBM2024-0730-41

A Transparent high-numerical-aperture photoacoustic microscopy system for brain functional imaging

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Abstract: The unique feature of optical-resolution photoacoustic microscopy (OR-PAM) lies in its capacity to provide high-resolution imaging of microvasculature without relying on exogenous agents. This capability exhibits remarkable potential for research into brain imaging. However, an ongoing challenge is the fabrication complexity and limited availability of self-focusing high-frequency piezoelectric transducers with a high numerical aperture (NA) across a broad frequency range. Here, as a novel approach to high-quality microvasculature imaging, a dual-wavelength fiber-coupled OR-PAM system is demonstrated on the mouse ear and brain in vivo. Furthermore, assisted with a novel transparent high-frequency (≥40MHz) ultrasound transducer with a high NA of 0.54 and broadband over 70% (-6 dB), the dual-wavelength PAM system enable the clear visualization of blood vessels and oxygen saturation in the brains of mice, providing functional insight on living tissue. The new ultrasound transducer offers enhanced performance, providing higher peak-to-peak sensitivity and higher NA while maintaining wide bandwidth. The novel integration of these technologies expands our imaging capacity, making the transparent high NA photoacoustic microscopy system a reliable tool for applications in brain science and research on neurological diseases.

[TP-15] PIBM2024-0731-26

Non-regular handheld transducer array for improved video-rate ultrasound and photoacoustic imaging

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Abstract: Linear-array dual-modality photoacoustic (PA) and ultrasound (US) imaging can provide

complementary anatomical structure and excellent molecular contrast, making it highly suitable for handheld clinical screening and disease diagnosis. However, despite the portability of clinical linear-array imaging systems, they still suffer from low lateral resolution and a limited field of view in dual-modality imaging, and some vascular features are usually absent in PA imaging. Here, we develop a dual-modality system equipped with specially constructed handheld transducer array. The transducer array consists of a linear transducer array with 64 elements evenly distributed in the middle, flanked by two arc-shaped transducer arrays with 32 elements each on either side. All elements are designed to be cylindrically focused in the elevational direction. We also develop a spatially corrected beamforming algorithm to improve image quality for the non-regular transducer array. The imaging system achieves co-registered high-speed US and multi-spectral PA imaging (>50 Hz) simultaneously. Phantom experiments, mouse heart pulsation imaging, and human trials demonstrate that the new imaging system and method significantly enhance image quality, revealing its potential clinical value.

[TP-16] PIBM2024-0731-48

High-Speed Multispectral Photoacoustic Computational Microscopy for Large-Scale Biomedical Imaging

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Abstract: Photoacoustic computational microscopy (PACM) is a promising imaging modality that combines the advantages of high depth-to-resolution ratio (1/200) and rich optical contrast by using several computational methods such as synthetic aperture. However, the application of PACM is constrained by various factors. Firstly, the lack of fast tunable lasers leads to prolonged multi-wavelength imaging times, inevitably introducing motion artifacts. Secondly, the existing PACM are limited by narrow tuning range of spectra range, which restricts the molecular imaging capabilities of PACM. To address the challenges mentioned above, we have developed a high-speed multispectral photoacoustic computational microscopy (HSM-PACM) equipped with a customized high-sensitivity hollow self-focusing transducer and a per-pulse tunable laser with broadband spectra (670nm-2500nm) at 100Hz. By utilizing the system combined with the adaptive synthetic aperture method, we provide accurate co-registered multispectral data, which allows for fast high-fidelity quantification of chromophores such as hemoglobin, melanin, lipid and fluorescent protein markers. In summary, the proposed HSM-PACM provides a powerful research and diagnostic method for biological and clinical medicine studies.

[TP-17] PIBM2024-0818-2

Score-based generative model-assisted information compensation for high-quality limited-view reconstruction in photoacoustic tomography

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Abstract: Photoacoustic tomography (PAT) regularly operates in limited-view cases owing to data acquisition limitations. The results using traditional methods in limited-view PAT exhibit distortions and numerous artifacts. Here, a novel limited-view PAT reconstruction strategy that combines model-based iteration with score-based generative model was proposed. By incrementally adding noise to the training samples, prior knowledge can be learned from the complex probability distribution. The acquired prior is then utilized as constraint in model-based iteration. The information of missing views can be gradually compensated by cyclic iteration to achieve highquality reconstruction. The performance of the proposed method was evaluated with the circular phantom and in vivo experimental data. Experimental results demonstrate the outstanding effectiveness of the proposed method in limited-view cases. Notably, the proposed method exhibits excellent performance in limited-view case of 70◦ compared with traditional method. It achieves a remarkable improvement of 203% in PSNR and 48% in SSIM for the circular phantom experimental data, and an enhancement of 81% in PSNR and 65% in SSIM for in vivo experimental data, respectively. The proposed method has capability of reconstructing PAT images in extremely limited-view cases, which will further expand the application in clinical scenarios.

[TP-18] PIBM2024-0820-13

Dual-band fiber ultrasound transducer array for photoacoustic computed tomography with high resolution and deep penetration

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Abstract: Photoacoustic imaging with high resolution and deep-penetration imaging is crucial to brain functionality study and disease diagnosis. To achieve deep penetration, photoacoustic computed tomography (PACT) commonly employs low-frequency ultrasound transducer array to reduce the frequency-dependent ultrasound attenuation. But the low-frequency photoacoustic signal loses the fine structure information, causing degradation in the spatial resolution. Here, we have developed a PACT system based on a dual-band fiber-laser ultrasound transducer array. By tuning the coating parameters of the fiber laser, the frequency response can be tailored through the ultrasound coupling between the silica fiber and the surrounding polymer

coating. The dual-band fiber-laser ultrasound transducer covers the low frequency region near ~2.5 MHz and high frequency region near ~20 MHz with a pressure detection limit as low as ~ 10 Pa, which allows simultaneous measurement of both low-frequency signals from deep tissues and high-frequency signals from fine structures. An arc-shape PACT array system with 150° angular coverage is constructed by eight dual-band fiber transducers, which demonstrates the capability for whole-brain imaging of mice with depths up to ~1 cm and nearly isotropic spatial resolution (~135 μm) for the cerebral cortex vessels. This system is further utilized to visualize oxygen saturation of hemoglobin within the entire mouse brain, glioblastoma-grown brain regions, and human fingers, demonstrating its great potential for biomedical and clinical applications.

[TP-19] PIBM2024-0715-2

Label-free identification of fibrotic focus in breast tumor microenvironment using multiphoton microscopy

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Abstract: Breast cancer, the most common malignant tumor among women worldwide, is influenced in its development and progression by a variety of factors in tumor microenvironment. Fibrotic focus (FF), a critical pathological feature within tumor microenvironment, is closely correlated with the invasiveness, malignancy and clinical pathological prognostic features of tumor. Therefore, accurately identifying FF for the early diagnosis, formulation of treatment strategies and prognostic assessment of breast cancer remains crucial importance. Multiphoton microscopy (MPM) is an advanced biomedical imaging technique that relies on intrinsic nonlinear optical effects of biological tissues, such as two-photon excited fluorescence (TPEF) and second-harmonic generation (SHG). This technology enables real-time observation and label-free assessment of tissue slices without the need of staining, providing high-resolution images of biological tissues. In this study, we utilized MPM for label-free identification of FF in breast cancer, following by image data processing to extract collagen features. The results indicate that MPM is able to quickly and accurately detect this pathological feature within the tumor microenvironment without the use of exogenous contrast agents and can even identify varying degrees of fibrotic focus. Featuring rapid imaging and minimal tissue damage, MPM demonstrates great potential as an emerging tool in label-free monitoring of various pathological features in tumors.

[TP-20] PIBM2024-0718-1

Proximal-scanning BM-mode endoscopic OCT elastography

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Abstract: Proximal rotary scanning is predominantly used in the clinical practice of endoscopic and intravascular OCT, mainly because of the much lower manufacturing cost of the probe compared to distal scanning. However, proximal scanning causes severe beam stability issues (also known as non-uniform rotational distortion, NURD), which hinders the extension of its applications to functional imaging, such as OCT elastography (OCE). In this study, we demonstrate the abilities of learning-based NURD correction methods to enable the imaging stability required for intensity-based proximal-scanning endoscopic OCE. Compared with the previous learning-based NURD correction methods that use pseudo distortion vectors for model training, we propose a pipeline to extract real distortion vectors from a specific endoscopic OCT system, and validate its superiority in accuracy. We further verify its effectiveness in elastography calculations (digital image correlation and optical flow) and the advantages of our method over other NURD correction methods. Considering the need for an appropriate mechanical stimulus, here we utilize the air pressure of a balloon catheter, which is common to percutaneous interventional procedures, our endoscopic OCE could effectively differentiate between areas of varying stiffness of atherosclerotic vascular phantoms. This strategy does not require changes to the OCT endoscope design and has a low need for synchronization. Compared with the existing endoscopic OCE methods that can measure only in the radial direction, our method first achieves 2D BM-mode displacement/strain distribution in both radial and circumferential directions. We think it is promising for many clinical applications such as on-site diagnosis, intraoperative monitoring, and therapeutic evaluation.

[TP-21] PIBM2024-0718-2

Speckle decorrelation rate for visualizing therapeutic thermal field with OCT

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Abstract: OCT is transitioning from a diagnostic tool to one that also aids in treatment. However, structural imaging is difficult to visualize the therapeutic field of minimally invasive thermal treatment, such as laser or radiofrequency ablation, due to the fact that the optical properties of the tissue are less altered during the temperature increase prior to denaturation of the tissue (~50 ℃). Here we propose to use speckle decorrelation rate, as a new contrast mechanism for visualizing the therapeutic thermal field. We performed ex vivo tissue experiments on an integrated laser ablation-OCT surveillance system. We found that, compared with the speckle decorrelation employed in existing works, the speckle decorrelation rate could be a more robust indicator: It has higher signal-to-noise ratios and is less sensitive to the selection of time interval (used in the decorrelation calculation). The superiority of our method has been verified on different types of biological tissues. Besides, it is label-free and can be readily applied to various setups of OCT systems. We think our method may be contributed to improving the precision and safety of thermal therapies.

[TP-22] PIBM2024-0718-3

Depth-of-focus extension in endoscopic OCT via computer-generated holography

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Abstract: This study presents a novel method for extending the depth of focus (DOF) in endoscopic Optical Coherence Tomography (OCT) by integrating computer-generated holography (CGH). The technique addresses the limitations associated with probe size, resolution, and imaging range, offering a high-uniformity and high-efficiency solution. Utilizing CGH's multi-dimensional light-field modulation, we precisely control the intensity distribution of the OCT probe light's off-axis components, eliminating the need for an objective lens and enabling direct fabrication at the distal end of a single-mode fiber through femtosecond laser two-photon 3D printing. The method involves dividing the target needle-shaped beam into layers, applying the Gerchberg-Saxton algorithm for phase recovery to match the incident light's amplitude and achieve a desired energy distribution for improved focusing efficiency. Numerical simulations and experiments confirm the method's effectiveness, with a significant increase in focusing efficiency from approximately 42% to 67% compared to existing methods. The fabricated probe, with a 5 μm focal spot and a DOF of 224 μm, significantly outperforms a Gaussian beam of similar spot size, which has a DOF of only 67 μm. OCT imaging with the developed probe maintains high resolution across the entire range, contrasting with the rapid resolution loss due to defocusing observed in Gaussian beams. This study's CGH-based method for DOF extension in endoscopic OCT demonstrates superior performance and potential for clinical applicability, with future work focusing on increasing diffractive optical element height levels, optimizing CGH algorithms, and addressing astigmatism and aberrations.

[TP-23] PIBM2024-0718-4

An embedded clinical decision support system for OCT

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Abstract: Large Language Models (LLMs) are revolutionizing various aspects of our lives. Integrating LLMs into Optical Coherence Tomography (OCT) devices could significantly assist doctors by offering diagnostic

and treatment recommendations, particularly in situations where medical expertise is scarce. Unlike artificial intelligence (AI) models that provide diagnostic conclusions opaquely, LLMs enhance the safety and efficacy of AI-assisted diagnosis and treatment through interactive human-computer dialogue. However, due to the imperative to protect patient privacy and ensure data security, OCT devices in healthcare settings are commonly operated offline. This limitation prevents the implementation of LLMs in an online environment, contrasting with platforms like ChatGPT or Kimi. Additionally, the operation of current LLMs demands substantial graphics memory, posing a significant challenge for OCT devices that already require considerable graphics memory for tasks such as data acquisition, rendering, and real-time display. In this paper, we introduce ChatOCT, an embedded clinical decision support system with specialized knowledge in OCT and related medical fields, designed to operate offline and with minimal computational resources. We propose a framework for its development, encompassing OCT knowledge injection, Q&A-based clinical instruction tuning, and model compression techniques. The superiority of our models, both the original one and a 79% compressed version, has been independently confirmed by ChatGPT (GPT-4) and two clinical ophthalmologists. We envision that ChatOCT could significantly elevate the intelligence and adoption of OCT technology.

[TP-24] PIBM2024-0718-5

Deep learning for robotic-assisted OCT

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Abstract: Robotics has been leveraged in OCT to extend the scale of imaging. It still has two technical issues should be addressed before practical applications: (1) For the probe-to-surface control, the rule-based feature extraction is susceptible to imaging artifacts of OCT. (2) The use of ultra-fast swept-sources improve the speed of scanning, but leads to a significant increase in system cost. To tackle these issues, we employ deep learning for automatic feature extraction and compressive sensing. A U-shape segmentation network, trained on OCT B-scans with various artifacts, demonstrates the ability to accurately detect imaging object surfaces, we can use the surface of the segmented object for the pose estimation of our robotic arm. For cost-effective data acquisition, we use a sampling density lower than the Nyquist sampling theorem and reconstruct high-resolution images in real-time using a trained cycle-consistent generative adversarial network. Our approach reduces the need for expensive hardware while maintaining acquisition speed. The experimental setup includes a 6-DOF robotic arm and an 840-nm spectral domain OCT system, and the results show that our deep-learning-assisted OCT system can reliably segment objects under OCT artifacts and reconstruct high-resolution images from low-density samples, significantly increasing scanning speed and reducing system costs compared to other robotic-assisted OCT systems. We think the adoption of our methods may promote more medical and industrial applications for the robotic-assisted OCT.

[TP-25] PIBM2024-0718-6

Fast OCT deconvolution using a light-weight CNN

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Abstract: The broad application of deconvolution in OCT is hindered by (1) speckle-noise-induced deconvolution artifacts and (2) the time-consuming deconvolution process. To address these issues, we propose a deep-learning-based method for fast OCT deconvolution, which include a speckle noise reduction module and a deconvolution module. We also introduce a lightweight convolutional neural network (CNN) for accelerating the inference processes. With similar performance on artifact-free deconvolution, our method is 2,777 times faster than the state-of-the-art iterative deconvolution algorithm and achieves an average inference time of 1.41 ms for a single B-frame. The number of parameters of our proposed CNN architecture is 2.17 times less than that of U-Net, and the inference is 5 times faster. For the discrete objects in OCT images, our method achieves 50.58% and 60.36% improvements in axial and transverse resolutions, respectively. For the continuous objects, our method achieves an average 13.91 dB improvements in the contrast-to-noise ratio.

[TP-26] PIBM2024-0722-1

Research on defect fingerprint compensation method based on Optical Coherence Tomography

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Abstract: In view of the problem that traditional fingerprint devices are prone to incomplete fingerprint information due to surface noise pollution (such as scratches and peeling) when collecting fingerprints on the tip of the finger, a method using optical coherence tomography (OCT) to collect subcutaneous internal fingerprints to compensate the external fingerprint information is proposed. In the experiment, a traditional fingerprint device is used to obtain the external fingerprint of the fingertip, and defective fingerprint information was obtained by erasing some information of the fingerprint with image processing technology. Then, OCT is used to collect the subcutaneous internal fingerprint, and the features are compared with the external fingerprints. The subcutaneous internal fingerprint is rotated to align with the external fingerprint. Finally, image fusion is used to complete the information of the external fingerprint on the fingertip. The experimental results show that the missing external fingerprint information can be completely replaced by the subcutaneous internal

fingerprint information at the same location.

[TP-27] PIBM2024-0723-2

Stable detection of hepatocellular carcinoma using FAP$^+$ CAFs peptide-targeted NIR-I/II fluorescence imaging: a clinically translatable approach

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Abstract: Background: Cancer-associated fibroblasts (CAFs) are the primary stromal component of the tumor microenvironment in hepatocellular carcinoma (HCC), associated with tumor progression and recurrence risks. Fibroblast activation protein (FAP) is a key biomarker of CAFs. However, there is limited evidence on using FAP as a target in near-infrared (NIR) fluorescence imaging for HCC. Thus, this study aims to develop a novel NIR fluorescent imaging strategy targeting FAP$^+$ CAFs in HCC.

Methods: We synthesized the ICG-FAP-TATA probe by conjugating a cyclization anti-FAP peptide with the near-infrared fluorescent dye indocyanine green (ICG), capable for NIR window I (NIR-I, 700-900 nm) and II (NIR-II, 1000-1700 nm) imaging. Its efficacy in lesion localization and other potential applications was evaluated.

Results: *In vivo* imaging of HCC mouse models revealed that ICG-FAP-TATA specifically targeted FAP$^+$ CAFs in the stroma and detected differences in CAFs loading within lesions. *Ex vivo* incubation of tumor tissues with ICG-FAP-TATA provided stable, high-contrast fluorescence imaging for tumor lesions in both subcutaneous and orthotopic HCC models with different cell lines and liver backgrounds (n=60). The tumor-to-background ratio (TBR) of the tumor mouse models was significantly higher for NIR-II than for NIR-I imaging (3.89±1.27 vs. 2.64±0.64, p<0.05). Moreover, NIR-I/II imaging of fresh tissues from seven HCC patients undergoing surgery, when incubated with ICG-FAP-TATA, effectively targeted tumor lesions through high FAP expression in CAFs, as validated by H&E and IHC staining. The feasibility of rapid HCC imaging within 20 minutes after ICG-FAP-TATA incubation in *ex vivo* tissue was demonstrated. Additionally, ICG-FAP-TATA exhibited good biosafety both *in vitro* and *in vivo*.

Conclusion: This study presents a rapid and effective method for locating FAP$^+$ CAFs and detecting HCC lesions, offering a promising new approach with translational potential for imaging HCC.

[TP-28] PIBM2024-0724-3

A novel dual-targeting pH-responsive autologous neutrophil cell membrane biomimetic drug delivery system targeted to dissolve tumor stroma and fluorescently image the tumor area in HCC

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Abstract: Radical resection is considered to be the main treatment for hepatocellular carcinoma (HCC) patients to obtain long-term survival. But 60% patients are at the advanced stages during initial diagnosis and are not suitable for surgery. Immunotherapy can transform unresectable HCC into resectable HCC, which brings the possibility of cure for patients. However, due to the high heterogeneity of HCC and the tumor stroma barrier, the overall response rate of HCC patients is less than 20%. Molecular imaging technology is considered a promising tool for detecting residual lesions intraoperatively, but the hepatic uptake of contrast agents significantly hinders its application in liver tumors. Biomimetic nano drug delivery systems, due to their low immunogenicity and high specificity, are considered effective means to enhance therapeutic response and improve imaging efficiency. In this study, we developed a novel dual-targeting pH-responsive autologous neutrophil cell membrane biomimetic drug delivery system, PSMA/CXCL12-CHEMS-NE@ICG, which specifically targets and dissolves HCC stroma while enhancing fluorescence imaging efficiency in the tumor region.

PSMA/CXCL12-CHEMS-NE@ICG is composed of a modified pH-responsive vesicle targeting PSMA and the fusion of the human neutrophil cell membrane. In vivo imaging experiments on subcutaneous tumor-bearing animals showed that a fluorescent signal appeared in the tumor 3 hours after probe injection, and the tumor-to-background ratio (TBR) of the tumor reached its peak about 12 hours after injection. PSMA/CXCL12-CHEMS-NE@ICG is expected to achieve efficient drug delivery and highly specific lesion imaging for HCC, demonstrating great clinical application potential in improving intraoperative localization and image-guided surgery for HCC.

[TP-29] PIBM2024-0725-4

Image reconstruction based on Graph structure for MRI-guided diffuse optical tomography

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Abstract: Diffuse optical tomography (DOT) is a noninvasive and label-free imaging technique and has been widely used in breast cancer diagnosis and brain imaging. DOT can quantitatively measure the tissue functional information and the concentration of oxyhemoglobin, deoxyhemoglobin, and other components. However, the spatial resolution of DOT is low. Utilizing anatomical information from high-resolution imaging to guide DOT is an effective strategy to enhance the quality of reconstructed DOT image. In this study, graph structure is developed to fuse MRI images to guide DOT reconstruction (GRI). Firstly, we encode MRI grayscale image into graph structure information. Secondly, incorporate graph structure information is directly incorporated into DOT reconstruction as a weight matrix. The advantage of our method is that the graph structure can adapt to any tissue structure without segmenting MRI images, eliminating user intervention. The algorithm was validated with numerical simulation experiments . The results show that compared with the Tikhonov regularization algorithm, GRI can improve the mean square error (MSE) (16%), peak signal-to-noise ratio (PSNR) (10%) and structural similarity index measure (SSIM) (10%); compared with the popular Graph-

TV algorithm, MSE is improved by 12%, PSNR is improved by 10%, and SSIM is improved by 7%; compared with a imaging guided algorithm (DRI), MSE is improved by 10%, PSNR is improved by 7%, and SSIM is improved by 7%. Real patient experiments further confirm its feasibility.

[TP-30] PIBM2024-0725-5

The Impact of SNR Reduction on Tumor in Full-Ring Photoacoustic Tomography for Breast Cancer Imaging

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Abstract: Photoacoustic imaging has demonstrated promising potential in breast cancer tumor imaging and segmentation, particularly by leveraging the contrast provided by abnormal angiogenesis. This non-invasive technique has been explored in previous studies, showing its ability to detect and characterize breast tumors based on unique vascular patterns. However, clinical experiments have revealed challenges in imaging deep-seated breast tumors, with factors such as laser and ultrasound attenuation and noise levels impacting the quality of photoacoustic signals. This results in a poorer signal-to-noise ratio (SNR) compared to superficial large blood vessels, leading to reduced tumor contrast in reconstructed images and making it difficult for clinicians to visually identify tumors.

Despite progress, there remains a lack of research exploring the imaging characteristics of breast tumors at different stages from the perspective of angiogenesis. Understanding how vascular proliferation changes as a tumor progresses could improve tumor detection and characterization using photoacoustic imaging. Additionally, there is a need to establish specific performance requirements for accurate tumor identification, including investigating the impact of SNR reduction on tumor contrast and analyzing tumor morphological features using full-ring photoacoustic tomography systems with different in-plane resolutions.

To address these gaps, we conducted a study based on a simulation model of tumor vasculature, focusing on the impact of SNR reduction on tumor contrast and analyzing tumor morphological features. The results provide valuable insights into the potential of photoacoustic imaging for tumor identification and could contribute to advancing its application in clinical practice. By improving our understanding of breast tumor imaging characteristics at different stages and establishing specific performance requirements, we can enhance the accuracy and reliability of photoacoustic imaging for breast cancer detection and characterization.

[TP-31] PIBM2024-0725-6

Rotational Cherenkov-Excited Luminescence Scanned Tomography Reconstruction with Symmetry Vision Mamba

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Abstract: Rotational Cherenkov-Excited Luminescence Scanned Tomography (RCELST) is an emerging optical imaging technology that visualizes the distribution of luminescent quantum yield within the treated subject. This technology involves collecting luminescence signals resulting from the excitation of luminescence probes by Cherenkov emissions within the volume, induced by the rotational scanning of MV X-rays. These signals are mapped into a sinogram for reconstructing the distribution of luminescent quantum yield by neural networks. Vision Transformers (ViTs), as an effective deep learning algorithm known for capturing long-distance dependencies, have been utilized in medical image reconstruction tasks. However, the large scale of medical images, compounded by the quadratic complexity of ViTs, results in erratic and time-consuming reconstruction performance. Therefore, a more efficient algorithm is essential for reducing reconstruction time. In this study, we propose a Symmetry Vision Mamba (S-VM) to decrease time consumption while maintaining reconstruction accuracy. The S-VM employs Vision Mamba, which uses the theory of State Space Models (SSMs) to achieve global information extraction in the 2-dimensional sinogram signals. With linear computational complexity, S-VM considerably reduces the learning process when compared to Transformer algorithm. The S-VM also utilizes a symmetrical encoder, incorporating conv-stems to extract local features, enabling multi-scale feature fusion by sharing parameters between two encoder branches. The results from training on 10,000 sinogram signals demonstrate the effectiveness of the S-VM algorithm, achieving a peak signal-to-noise ratio (PSNR) of up to 38.67dB and a structural similarity index measure (SSIM) of 0.97. Meanwhile, reaching these accuracies on average takes S-VM 1.46 hours of training.

[TP-32] PIBM2024-0727-6

Ridge regression optical coherence tomography breaking through the theoretical axial resolution

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Abstract: Axial resolution is an important parameter that affects the image quality in OCT systems. As a traditional OCT image reconstruction method, the axial resolution of Fast Fourier Transform (FFT) is limited by the central wavelength and spectral bandwidth of the light source. Aiming to overcome the limitation of the spectral width of light source on the axial resolution, an OCT image reconstruction algorithm based on ridge regression model is proposed in this paper. In this method, the ridge regression model is trained by using the plane mirror interference spectrum and depth label, and the model between the interference spectrum frequency and depth is obtained. By bringing the plane mirror interference spectrum signals at different depths into the model, the depth signal of the plane mirror is reconstructed. The results show that the axial resolution of the algorithm is ~1.25 μm (theoretical value ~7.9 μm). At 2.5 mm, the axial resolution does not widen significantly with depth. In order to verify the effectiveness of the algorithm for complex samples, the image reconstruction of the gold nanoparticle phantom can display more details than the Fourier Transform, indicating that the algorithm improves the axial resolution of the FFT algorithm. Finally, so as to confirm the feasibility of the proposed algorithm on biological samples, the retinal interference spectrum is reconstructed. The

experimental results show that the proposed method can clearly display the retinal layer structure details compared with the Fourier Transform.

[TP-33] PIBM2024-0728-1

Personalized precision imaging of hepatocellular carcinoma *via* NIR-II fluorescent probe delivered by tumor-derived extracellular vesicles

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common malignant cancers worldwide, and radical surgical excision is still the most effective treatment. However, positive margins and residual tumor cells lead to a recurrence rate reaching 70% within five years after surgery. It's still a great challenge to achieve radical resection of HCC lesions. Molecular-targeted fluorescence imaging probes provide a promising solution to this challenge, but the high heterogeneity of HCC may limit their imaging effectiveness and clinical applicability. Tumor-derived extracellular vesicles (EVs) are excellent candidates for delivering imaging probes due to their stability, biocompatibility, and homologous targeting and homing capability. Here, we reported a novel imaging probe, ICG-EVs, using EVs as the carrier and Indocyanine green (ICG) as the fluorescent dye. This probe performed powerful functions for targeted imaging of tumor lesions in the second near-infrared fluorescence window (NIR-II, 1000-1700 nm). Experiments have confirmed that ICG-EVs have great biosafety at cellular and animal levels, loading ICG does not affect EVs' physicochemical properties and homologous targeting capability. ICG-EVs also displayed NIR fluorescence imaging characteristics similar to free ICG. Notably, tumor-derived EVs enhance tumor cellular uptake of ICG. By cross-validating in multiple human HCC cell lines and corresponding mouse subcutaneous transplanted tumor models, ICG-EVs exhibited precise targeting toward homotypic donor cells. *In vivo,* NIR-II imaging experiments in mice showed that fluorescence signals from tumor lesions started appearing 3 hours after probe injection, reaching a maximum tumor-to-background ratio (TBR) of approximately 5.07 at 48 hours. In summary, ICG-EVs is first applied to NIR-II fluorescence imaging in preclinical HCC models, highlighting their potential clinical application prospects as personalized targeted imaging probes. This strategy aims to overcome heterogeneity in HCC, enabling precise intraoperative tumor localization and defining infiltration boundaries to guide surgical resection, ultimately improving the overall prognosis for HCC patients.

[TP-34] PIBM2024-0728-2

Targeting CEACAM5 with Single-Chain Antibody Fluorescent Probes for Ex Vivo Precision Imaging of Colorectal Cancer and Liver Metastases

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Abstract: The challenge of accurately detecting micro-metastases of colorectal liver metastases contributes to a high postoperative 5-year recurrence rate of up to 70%. Molecular imaging has been widely recognized for its crucial role in aiding clinical decision-making. Fluorescent molecular probes labeled with antibodies have

become essential tools in fluorescence-guided surgery due to their excellent targeting performance. However, the large particle size of antibody-based specific targeting probes limits their effectiveness in liver tumors. CEACAM5 is highly and stably expressed in colorectal cancer. In this study, we developed a single-chain antibody（scFv） fluorescent-labeled molecular probe, scFv@CEACAM5-800CW, targeting CEACAM5. We demonstrated its ability to target CEACAM5-positive tumor cells at the cellular and *ex vivo* tissue levels.
Firstly, we verified the expression of CEACAM5 in normal intestinal and liver cells as well as in common colorectal cancer cell lines. Subsequently, confocal imaging of cell lines with high and low expression of CEACAM5 revealed that scFv@CEACAM5-800CW accumulated in the cell membrane regions of cells with high CEACAM5 expression, while no such accumulation was observed in negative controls. Furthermore, scFv@CEACAM5-800CW exhibited strong fluorescence in primary colorectal cancer lesions (n=3) and liver metastases (n=2) derived from patients, with significantly weaker fluorescence signals in adjacent normal tissues (intestine n=3, liver n=2).
The results preliminarily confirm the targeting ability of scFv@CEACAM5-800CW for CEACAM5 at the *ex vivo* level, indicating its potential for precise in vivo detection of colorectal cancer and liver metastases.

[TP-35] PIBM2024-0728-8

A theoretical model of laser speckle contrast imaging based on transmission illumination

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Abstract: Laser speckle contrast imaging (LSCI) is widely employed for mapping the spatio-temporal dynamics of blood perfusion in vivo and clinical theranostics, owing to its rapid imaging speed and the simplicity of wide-field recording. However, its application is limited by a superficial imaging depth and challenged in resolving microvascular structures. Although transmissive imaging can significantly improve the detecting depth and resolution, ballistic photons that transmit forward through tissue without scattering can cause significant errors in estimating the de-correlation time of scattering light related to blood flow speed when using the traditional theoretical model of LSCI. In this study, we developed a new theoretical model of transmissive temporal LSCI by extracting the scattered component from the total transmitted light. Based on this model, we proposed a long-short exposure transmissive temporal laser speckle imaging method to simultaneously image of angiography and blood flowmetry. The simulation and blood-intralipid phantom experiments confirmed the accuracy of our method in measuring flow velocity. In the *in vivo* experiments, the transmissive LSCI can simultaneously obtain blood flow speed and blood vessel morphology at capillary level in tissue with a thickness of hundreds of micrometers, such as mouse ear and dorsal skin. Furthermore, our method can correct the overestimation of the blood flow speed in non-vascular background tissues present in traditional model of transmissive LSCI. In conclusion, our new model of transmissive LSCI improves the accuracy and resolution of blood flow speed estimation, which may promote the broader application of LSCI in scientific research and clinical diagnosis and treatment.

[TP-36] PIBM2024-0729-2

Non-contact measurement of zebrafish heartbeat guided by OCT imaging

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Abstract: The heart is the first organ to develop in zebrafish, and its developmental process is similar to that of the human heart. Zebrafish are an important model for studying human heart disease, and the accurate quantification of zebrafish heartbeats is instrumental in elucidating the intricacies of cardiac function and the pathogenesis of heart diseases, thereby facilitating a comprehensive understanding of potential therapeutic avenues. However, traditional methods such as electrocardiograph make it difficult to measure the heart rate of zebrafish in water. In this study, optical coherence tomography (OCT) is employed to obtain high-precision images of the zebrafish heart area. These images are processed with an optical flow estimation algorithm to capture the motion information of the heart structure. Subsequently, a linear motion trajectory analysis algorithm is applied to fit waveforms to the extracted motion trajectories, enabling accurate computation of the zebrafish's heartbeat. The study demonstrates that this integrated approach enables high-precision, non-invasive measurement of zebrafish heartbeats, which can be used to monitor the changes in the zebrafish heartbeat induced by different anesthetic formulations.

[TP-37] PIBM2024-0729-9

Research on Single-port Endoscopic Theranostic Probe Based on OCT Guided Laser Ablation

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Abstract: With the development and progress of minimally invasive surgery, the diagnosis and treatment devices integrating OCT and laser ablation have important clinical significance in the diagnosis and treatment of natural lumen. To meet the demand for miniaturization of probes in the diagnosis, monitoring, and treatment of narrow living lesions during surgery and non-surgical procedures, the design method of OCT-laser ablation common optical path lateral scanning internal probe was proposed, and a single-sport endoscopic diagnosis and treatment probe was developed to achieve the integration of diagnosis and treatment for narrow biological tissue spaces. Firstly, based on the transmission theory of Gaussian optics, the waist position and Rayleigh range of the beam are explored, and the parameters of the probe combination element are selected to simplify the probe design; Next, based on the principle of spatial light reflection, explore the relationship between

MEMS scanning angle and laser spot position, and use MEMS micro motors to synchronize OCT scanning and laser ablation; Furthermore, using LightTools and COMSOL simulation software, investigate the dose-response relationship between ablation power, ablation spot size, and degree of damage; Finally, through the assembly and adjustment steps of lens bonding, dual path beam combining debugging, MEMS chip bonding, etc., the physical production of the probe is completed. Combined with imaging and ablation experiments, the rationality of the probe design is verified, achieving high-precision resection of tumor tissue. The probe can clearly see the leaf specimen lines, resolution plate stripes and human skin tissue, and the ablation has slightly effective. It has the advantages of long working distance, large scanning range, high resolution, compact structure, etc., which can lay the foundation for further research and clinical use of OCT-laser ablation probe in real-time imaging and treatment in vivo.

[TP-38] PIBM2024-0729-19

Assessment for pigmentation and vascularity of hypertrophic scar based on residual network

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Abstract: Hypertrophic scars are a type of pathological scar that can cause discomfort, pain, and itching. The assessment of hypertrophic scars depends largely on the clinician's long-term experience. Computer-aided assessment can greatly improve the efficiency and accuracy of scar assessment. In this paper, we propose a deep neural network-based assessment method for the degree of scar pigmentation and vascularity using real scar images. Firstly, a large amount of hypertrophic scar images were collected to produce a dataset including patients of all ages and the distribution of lesions in different parts of the body. These images were then scored on pigmentation and vascularity using the Vancouver Scar Scale (VSS). Then, the residual network model was proposed to evaluate the degree of scar pigmentation and vascularity according to the hypertrophic scar dataset. The degree of the pigmentation and vascularity were assessed respectively by two residual network models. The experimental results demonstrated that our method provides a reliable tool for the application of a scar diagnosis system.

[TP-39] PIBM2024-0730-7

A deep learning method for photoacoustic computed tomography based on sparse array sensor data

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Abstract: Photoacoustic tomography (PAT) is a new non-invasive biomedical imaging method based on the photoacoustic effect. It has the characteristics of high contrast of optical imaging and high resolution of acoustic imaging in deep tissues. In general, higher density two-dimensional annular or three-dimensional hemispherical transducer arrays can obtain higher quality imaging. However, the high cost and large size of the equipment hinder its practical clinical application. In this paper, we propose a deep learning method to reconstruct PA images in sparse array sampling. Different from some image-to-image deep learning methods which designed to remove distortions and artifacts using image dataset, this paper proposes a method to predict and complement the photoacoustic sensor channel data from sparse array sampling and then reconstruct images through conventional reconstruction algorithms. In the simulation results of the two-dimensional circular array, by predicting the sampling signals of 64 array elements to 256 array elements, the SSIM values of the reconstructed image and GT are improved by 12.83%, 6.78%, 21.46%, and 12.33% respectively, compared with the Convolutional Auto-Encode, U-net, linear interpolation, and XGBoost methods. The graphite and hair phantom experiments are also proved that the method is effective. We are now conducting phantom and in vivo experiments using 3D hemispherical arrays to verify the effectiveness of this approach in 3D reconstruction. The advantage of this method is that it does not require the collection of a large number of image data sets, but directly predicts and complete the signals received by the transducer. And then, the universal back-projection algorithm is used to remove the artifacts of the reconstructed image under sparse array sampling. It has the potential for low-cost and user-friendly detector arrays of clinical applications.

[TP-40] PIBM2024-0730-19

Large-DOF ultraviolet photoacoustic histologic imaging based on liquid crystal modulator

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Abstract: Gold standard hematoxylin and eosin (H&E) staining imaging of tissue slices requires preparations of micrometer-level formalin-fixed paraffin-embedded slices, which is incapable of providing intraoperative feedback because of time-consuming and labor-intensive procedures with significant delay from hours to days. Because DNA/RNA has strong optical absorption to ultraviolet (UV) light, the cell nucleus is captured with outstanding imaging contrast by photoacoustic microscopy (PAM) without introduction of exogenous contrast agents. However, a short depth of focus (DOF) in the traditional optical-resolution photoacoustic microscopy (OR-PAM) results in out-of-focus visualizations when imaging unsectioned tissue specimens with uneven surface topology, possibly causing inaccurate diagnostic reports. We propose a liquid crystal-based ultraviolet-PAM (UV-PAM) to produce a large DOF for imaging thick tissue samples with high resolution. Taking advantage of precisely manipulating the phases of the incident UV beam to modulate the photoacoustic illumination wavefront, the liquid crystal modulator enables the UV-PAM with an elongated DOF of ~290 μm while maintaining good lateral resolution of ~1.29 μm within the focal depth range. The novel system

demonstrate label-free histologic imaging of tissue slices that is well matched with the H&E staining views. Therefore, the liquid crystal modulator could empower the UV-PAM for obtaining non-destructive and label-free histological examinations.

[TP-41] PIBM2024-0730-20

Application of photon counting micro-CT in mice cerebrovascular imaging

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Abstract: The analysis of the anatomical structure and patency of cerebrovascular is an important way to understand brain disease. However, due to the small diameter of cerebral blood vessels and the influence of background tissues, it is difficult to extract cerebrovascular with conventional CT accurately. Photon counting CT (PCCT) is a newly developed spectral CT imaging technology that can directly extract the distribution of contrast agents such as iodine by using material decomposition, making it particularly suitable for cardiovascular imaging. However, there has been no research on the application of PCCT for cerebrovascular imaging. This study first tries to utilize a Photon counting micro-CT for in vivo imaging of mice cerebrovascular and explores the imaging impacts under different doses and injection methods of iodine contrast agents. The imaging results indicate that the minimum resolvable vessel diameter is less than 50 um, and the water-iodine material decomposition enabled direct extraction of mice cerebral blood vessels. The results showed that the photon counting micro-CT allows high-resolution imaging of mice cerebrovascular structures and direct extraction of vascular networks, making it a new powerful tool for the research of cerebrovascular diseases.

[TP-42] PIBM2024-0730-27

Non-invasive optical coherence tomography for dynamic acne progression monitoring and severity assessment

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Abstract: Acne vulgaris is a prevalent dermatological disorder stemming from a complex interplay of factors, including sebum hypersecretion, propionibacterium acnes colonization, hyperkeratosis, and inflammatory responses. Traditional pharmacodynamic methods lack the capacity for dynamic, non-invasive in vivo

monitoring of acne progression and severity. This study aimed to develop a murine model of acne vulgaris to elucidate its pathological mechanisms and quantitatively evaluate disease severity using non-invasive imaging techniques. We employed optical coherence tomography (OCT) in conjunction with microscopy to scrutinize the complete life cycle of acne lesions. Microscopy provided detailed observations of the microstructural features of the skin surface in murine models, while OCT enabled an assessment of skin structural changes. Our findings indicate epidermal hyperplasia associated with acne development, followed by scab formation during the reparative phase. Integration of deep learning algorithms allowed for precise quantification of epidermal and scab thickness variations. This novel approach to acne evaluation may refine the precision of clinical drug selection and enhance therapeutic efficacy.

[TP-43] PIBM2024-0730-33

A robust X-ray energy spectrum estimation method for PCCT based on a few-parameter model

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Abstract: Photon-counting computer tomography (PCCT) has emerged as a promising imaging technique with the capability to offer novel clinical applications. Accurately determing the system's X-ray energy spectrum is of significant importance, given that the fundamental concept of PCCT imaging relies on the variance in attenuation of materials under a range of X-ray energy spectrum. Nonetheless, achieving a stable and precise solution continues to be a formidable challenge. In this work, we propose a novel method for X-ray energy spectrum estimation based on a more universally applicable few-parameter model, which has taken into account of the effects of both the X-ray source and photon-counting detector. The degree of freedom of the energy spectrum estimation problem is greatly reduced by decreasing the number of unknown variables in X-ray energy spectrum. Reducing the number of measurements not only cuts down on time expenses, but it also lessens the condition number of the system matrix. In addition, we formulate appropriate regularization terms based on the characteristics of the X-ray energy spectrum to enhance the stability of the solution. To assess the efficacy of the suggested method, we carry out both a simulation study and an experimental study. The conclusive results demonstrate that the proposed method is highly robust against different data noises and closely matches the actual measurement results.

[TP-44] PIBM2024-0730-36

The spatial distribution of tumor cells is an independent prognostic marker in breast cancer

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Abstract: The biological behavior of tumor cells is closely related to tumor invasion, but the relationship between the spatial distribution of tumor cells at the invasion boundary and prognosis is still unknown. In this study, we based multiphoton microscopy (MPM) to image the tumor-associated collagen signatures (TACS), a biomarker known to be associated with breast cancer prognosis, and captured 180μm × 180μm regions of interest (ROI) on its colocalization of hematoxylin and eosin (H&E) images. The deep neural network was used to extract the 51 microscopic features of the spatial distribution of tumor cells from H&E images. The least absolute shrinkage and selection operator (LASSO) regression was used to select the most robust features to build a prognostic score. Our results showed that the spatial distribution of tumor cells was a poor prognostic factor in univariate analysis, and was proved to be an additional histological variable with an independent influence on disease-free survival (DFS) in the multivariate analysis in patients with breast cancer. The area under the receiver operating characteristic curve (AUC) of the prognostic score was 0.784 in the training cohort and 0.717 in the validation cohort. The study suggested that the spatial distribution of tumor cells was an independent prognostic marker for DFS in breast cancer and can provide prognostic information for breast cancer.

[TP-45] PIBM2024-0730-38

Fast endoscopic optical coherence elastography system for *in vivo* assessment of reproductive tract

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Abstract: Sensitive and accurate diagnosis of female reproductive tract lesions is crucial for addressing infertility issues and alleviating population problems. Optical coherence elastography (OCE) technology, with its advantages of high spatial resolution, displacement detection sensitivity, and elasticity quantification accuracy, offers new possibilities for improving the diagnosis of reproductive tract lesions. However, there is

still a lack of mature endoscopic OCE systems for *in vivo*, quantitative elastic properties assessment of reproductive tracts. The current endoscopic OCE system is limited by imaging speed, making it difficult to provide precise and reliable results for *in vivo* imaging assessment of reproductive tracts. Poor phase stability and prolonged excitation duration hinder the improvement of imaging speed. This study presents a fast endoscopic OCE system with an M-scan rate of 500 Hz. The system utilizes a single 38-MHz high-frequency ultrasound transducer to provide acoustic radiation force, inducing rapid deformation in tissues and achieving efficient excitation for elastography. The system's phase stability was optimized to 10 mrad, capable of accurately tracking the process of tissue deformation. Owing to high excitation efficiency and phase stability, the excitation duration of the system is shortened, thereby speeding up the OCE imaging process. The system features a miniaturized endoscopic OCE probe with an outer diameter of only 0.9 mm (with a 1.2-mm protective tube during imaging), allowing it to enter narrow lumens for imaging. *In vivo* imaging experiment were conducted on the reproductive tracts of rats in this study, comparing the improvement in the system's *in vivo* imaging performance after enhancing the imaging speed. Experiment with varying degrees of uterine injury in rats were conducted, and OCE images were able to finely distinguish different degrees of injury. The imaging results were consistent with histological sections. This study revealed that endoscopic OCE has potential clinical significance for sensitive and accurate diagnosis.

[TP-46] PIBM2024-0731-1

Innovative Confocal Endoscope for Real-Time Sub-Micron In Vivo Imaging

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Abstract: The confocal endoscope represents a cutting-edge in vivo imaging tool, providing real-time histopathological visualization at the cellular level, which is crucial for prompt and accurate surgical assessments. In the medical field, the need for miniaturization in endoscope design is driven by the limited space within working channels. This study introduces an innovative fiber optic scanner that exploits asymmetric fiber bending stiffness, resulting in a confocal probe with an ultrathin diameter of just 2.4 millimeters. This breakthrough probe achieves a sub-micron resolution of 0.98 μm, a frame rate of 8 fps, and an imaging range exceeding 130 μm, all while operating efficiently at a driving voltage of ≤ 30Vp-p. We conducted long-term imaging on live mice to validate the imaging capabilities.

[TP-47] PIBM2024-0731-10

Correction of non-uniform rotational distortion in proximally controlled endoscopic OCT using microfluidic phantom

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Abstract: In endoscopic OCT systems, the imbalance in torque load during rotational scanning will lead to non-uniform rotation of the distal probe, inevitably resulting in Non-Uniform Rotational Distortion (NURD) in the images. NURD can cause image translation and stretching or compression issues at arbitrary positions in OCT images, leading to misalignment of image information and impeding the implementation of endoscopic OCTA. In high-speed distal scanning OCT system, the instantaneous rotational speed of the micro-motor's metal struts was measured for OCT data resampling, enabling NURD correction, and OCTA was succefully realized. In proximal scanning, NURD is a more serious problem due to torque transmission over longer distances, resulting in asymmetric friction at different positions. In recent years, local block matching (LBM) and improved Features from Accelerated Segment Test (FAST) algorithms were used to solve NURD in B-scan images in proximal controlling OCT system. Cross-sectional OCTA was succefully implemented. In this paper, Global registration and A-line registration were used to correct NURD in continuous rotation and retraction of proximally controlled OCT imaging. Global registration is used to correct extensive NURD in B-scan images and A-line registration is applied for fine correction of minor NURD. Results from microfluidic data collected under the same position and retraction conditions demonstrate the effectiveness of NURD correction, and *en face* OCTA imaging was realized for the first time in a proximally controlled endoscopic OCT.

[TP-48] PIBM2024-0731-19

Diagnostic Methods for Multimodal Medical Image Fusion in Bladder Cancer

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Abstract: We developed a multimodal diagnostic method for bladder cancer using stimulated Raman scattering (SRS) microscopy. This method integrates chemical specificity and structural imaging with traditional pathological images for comprehensive analysis. By combining SRS images with pathological information such as H&E staining images, we achieved high-speed imaging and precise identification of bladder cancer tissues. The diagnostic model, trained on multimodal data from numerous patient samples, enables accurate diagnosis and analysis of pathological images, further allowing the assessment of muscularis infiltration and its specific grade. Additionally, our method facilitates detailed examination of tumor malignancy and evaluation of surgical

margins, promoting real-time intraoperative diagnosis.

[TP-49] PIBM2024-0731-21

Deep red light driven hydrogen evolution by heterojunction polymer dots for diabetic wound healing

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Abstract: Hydrogen as a therapeutic agent has attracted a great deal of attention because of its superior therapeutic outcome on many diseases, including inflammatory injury, tumors, metabolic disorders, and neurological diseases. Photocatalytic hydrogen evolution has emerged as a promising strategy for hydrogen production and delivery. We developed small heterojunction polymer dots (Pdots) with deep-red light catalyzed H_2 generation for diabetic skin wound healing. The Pdots with donor/acceptor (D/A) heterojunctions showed remarkably enhanced photocatalytic activity as compared to the donor (PTB7-Th) or acceptor (EH-IDTBR) nanoparticles alone. We encapsulate the Pdots and ascorbic acid (AA) into liposomes to form Lipo-Pdots nanoreactors, which selectively scavenge •OH radicals in live cells and tissues under 650 nm light illumination. According to the experiment results, the antioxidant capacity of the heterojunction Pdots was determined to be ~10 times higher than that of the single-component Pdots. Cellular assays and mouse paw studies indicated that the Lipo-Pdots nanoreactors under the deep-red 650 nm light irradiation apparently eliminated LPS-induced ROS in macrophages and mitigate subcutaneous inflammation. Under a light dose of 360 J/cm^2, which is comparable to those in photodynamic therapy, the Lipo-Pdots effectively scavenged •OH radicals and suppressed the expression of pro-inflammatory cytokines in skin tissues, thereby accelerating the healing of skin wounds in diabetic mice. This work provides a useful strategy for safe and effective treatment of diabetic foot ulcers.

[TP-50] PIBM2024-0731-36

Model control of corneal topography during refractive surgery: validation on artificial eyes

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Abstract: Purpose. Optimize the surgical cutting mode and control the change in corneal topography induced by biomechanical effect during refractive surgery.

Method. Based on the topography and mechanical characteristics of the target, a finite element analysis model was established to simulate the refractive cutting process, analyze and compensate the biomechanical effects, and verify them on a measurable artificial eye device.
Result. In the laser cutting experiment of artificial eye, the finite element analysis model based on our method can accurately predict the change of corneal curvature. The guided surgical cutting model can compensate for 70% of the undercorrection caused by biomechanical effects.
Conclusions. The accuracy of the finite element analysis model in the artificial eye model has been verified, and the method has a potential application prospect in the field of precision development of refractive surgery.

[TP-51] PIBM2024-0731-44

Research on muscle magnetic imaging device based on optically pumped magnetometer

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Abstract: The assessment of muscle activity is essential in nowadays diagnosis of peripheral muscle and nerve diseases, in fundamentals of movement neuroscience and in technologies for motor rehabilitation. Conventionally, the muscle activity is recorded and analysed electrically with Electromyography (EMG) . However, the electric signals suffer from poor spatial resolution and sensors implanted in the muscle face biocompatibility issues. In this work, we demonstrate a high sensitivity and spatial resolution optically pumped magnetometers measurement system for muscle magnetic measurement. First, a spin-exchange-relaxation-free optically pumped magnetometer based on single-beam configuration system is developed. After optimizing parameters that significantly affect the performance, the magnetometer sensitivity is better than 20 fT/ √Hz, the bandwidth is 0.1-185Hz, and the dynamic range is ±5nT, which can meet the requirements of muscle magnetic measurement. Moreover, we design a portable and movable magnetic shielding device. After applying monopolar square wave pulse stimulation signals to the ulnar nerve and median nerve of the subject, the magnetometer captures the magnetic signals of the elbow muscles in two orthogonal directions. This study can provide muscle activity data support for sports biomechanics research and promote the development of sports science.

[TP-52] PIBM2024-0731-49

A fluorescent probe for investigating the level of ONOO- associated with pharmacodynamic assessment of liver injury

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Abstract: Drug-induced liver injury (DILI) is a common liver disease caused by drug overdose due to toxicity of the drug itself and/or its metabolites. Serologic testing is currently the most widely used clinical diagnostic method for DILI. In this context, it is particularly urgent to develop a reliable method based on other biomarkers for real-time dynamic monitoring of DILI, which will help to reveal the pathogenesis of DILI and realize effective evaluation of treatment effects. In addition, the development of effective hepatotoxicity screening probes is essential during drug development in order to validate the safety of healthcare and the efficacy of drugs. Our probe monitors the protective effects of hepatoprotective drugs through hepatic detoxification mechanisms, in order to be able to screen the most appropriate drugs for the treatment of DILI. More importantly, our probe is expected to be used in the diagnosis and treatment of hepatocellular carcinoma.

[TP-53] PIBM2024-0801-1

Quantitative OCE-based assessment of femtosecond laser-induced elasticity changes towards visual accommodation in presbyopia treatment

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Abstract: Femtosecond laser-induced optical breakdown has been widely used in ophthalmic refractive surgery, but most procedures focus only on tissue dissection within the cornea to change curvature for refractive correction. Presbyopia, on the other hand, is an age-related loss of regulation of the eye's lens and is highly prevalent in the middle-aged and elderly population. When presbyopia occurs, the fibrous structure of the lens continues to grow, resulting in hardening of the lens tissue, inability of the peripheral ciliary muscles to squeeze the lens inward to thicken it, and difficulty in seeing at near, i.e., deterioration of visual accommodation. It has been shown that optical breakdown by femtosecond laser inside the crystalline lens, which produces several gliding planes through layers of tiny cavitation bubbles, seems to increase the flexibility of the lens. However, specific quantitative measurements of mechanical parameters have been lacking in this class of methods. We therefore propose a method for femtosecond laser spinning of the lens interior and a quantitative assessment of mechanical parameters based on optical coherence elastography (OCE) to quantify the effect that fs laser induced, with preliminary experiments on both phantoms and in-vitro porcine eyes.

[TP-54] PIBM2024-0817-1

Dark-based Optical Sectioning assists Background Removal in Fluorescence Microscopy

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Abstract: In the realm of fluorescence microscopy, a persistent challenge is defocused backgrounds that obscure cellular details and introduce artifacts or misclassification, impeding new biological discoveries. We introduce Dark sectioning, a pioneering de-background method that leverages dark channel principles and dual frequency separation to provide single-frame optical sectioning. Unlike denoising or deconvolution techniques that focus on noise reduction and resolution enhancement, Dark sectioning specifically targets and removes out-of-focus backgrounds, thereby significantly improving image clarity and fidelity. Our method has been rigorously validated across various microscopy modalities, demonstrating its high-fidelity results and ability to markedly improve segmentation accuracy in deep tissue imaging. It stably improves the signal-to-background ratio and structural similarity index measure of images by approximately 10-fold. Validated by widefield-confocal joint microscopy, multi-mode structure illumination microscopy (SIM), and one/two-photon joint microscopy, Dark sectioning shows the high-fidelity and complements those microscopies with optical sectioning and minimal artifacts. We further demonstrate its potential to improve the segmentation accuracy in deep tissues, resulting in better recognition of the neurons in the mouse brain and accurate assessment of nuclei in three-dimensional prostate lesions. Furthermore, the generalization of Dark sectioning is proved by the compatibility with many other microscopes such as light-filed, stimulated emission depletion microscopy, etc., and processing algorithms including deconvolution, super-resolution optical fluctuation imaging, etc. As an open-source and universally applicable solution, Dark sectioning promises to be a significant advancement for the field, facilitating clearer visualization and segmentation in biological studies, for both conventional and state-of-the-art fluorescence imaging techniques.

[TP-55] PIBM2024-0818-3

Noise-insensitive defocused signal and resolution enhancement for optical-resolution photoacoustic microscopy via deep learning

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Abstract: Optical-resolution photoacoustic microscopy suffers from narrow depth of field and a significant deterioration in defocused signal intensity and spatial resolution. Here, a method based on deep learning was proposed to enhance the defocused resolution and signal-to-noise ratio. A virtual optical-resolution photoacoustic microscopy based on *k*-wave was used to obtain the datasets of deep learning with different noise levels. A fully dense U-Net was trained with randomly distributed sources to improve the quality of photoacoustic images. The results show that the PSNR of defocused signal was enhanced by more than 1.2 times. An over 2.6-fold enhancement in lateral resolution and an over 3.4-fold enhancement in axial resolution of defocused regions were achieved. The large volumetric and high-resolution imaging of blood vessels further verified that the proposed method can effectively overcome the deterioration of the signal and the spatial resolution due to the narrow depth of field of optical-resolution photoacoustic microscopy.

[TP-56] PIBM2024-0819-8

Compressed single-shot 3D photoacoustic imaging with a single-element transducer

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Abstract: Three-dimensional (3D) photoacoustic imaging (PAI) can provide rich information content and has gained increasingly more attention in various biomedical applications. However, current 3D PAI methods either involves pointwise scanning of the 3D volume using a single-element transducer, which can be time-consuming (e.g., photoacoustic microscopy), or requires an array of transducers, which is known to be complex and expensive (e.g., photoacoustic computed tomography). By utilizing a 3D encoder and compressed sensing techniques, we develop a new imaging modality that is capable of single-shot 3D PAI using a single-element transducer. The proposed method is validated with phantom study, which demonstrates single-shot 3D photoacoustic imaging of different objects and 3D tracking of a moving object. After one-time calibration, while the system could perform single-shot 3D imaging for different objects, the calibration could remain effective for over 7 days, which is highly beneficial for practical translation. Overall, the experimental results showcase the potential of this technique for both scientific research and clinical applications.

[TP-57] PIBM2024-0819-9

High-precision measurement of tissue optical properties on complex surfaces using multi-frequency and multi-phase method

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Abstract: We propose an advanced Spatial Frequency Domain Imaging (SFDI) method that significantly enhances the measurement of tissue optical properties in complex surface morphologies. By introducing a multi-frequency and multi-phase method, we address the limitations of traditional three-phase unwrapping techniques in handling surfaces with steep height variations. Combining phase-shifting profilometry with spatial frequency domain imaging, our system accurately captures 3D shapes and optical properties of tissues, such as absorption (μ_a) and reduced scattering (μ_s'), with minimal additional computational effort. This work lays the foundation for more precise quantitative imaging applications, particularly in surgical environments where accurate 3D shape measurement and optical property analysis are crucial.

[TP-58] PIBM2024-0819-12

A fast time-domain diffuse optical tomography system enabled by projection view optimization and surface extraction

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Abstract: Time domain diffuse optical tomography (TD-DOT) is a non-invasive imaging technique that uses near-infrared light to map the three-dimensional distribution of the internal optical properties of biological tissues. Compared to other modes of DOT techniques, i.e., continuous wave and frequency domain DOT, TD-DOT offers the richest measurement information, thus achieving superior image resolution and quantitative accuracy. However, conventional TD-DOT systems face several challenges. One significant issue is the missing surface information which is required as the prior knowledge for the following image reconstruction. Additionally, the large amount of data collected by the time resolved detector increases both the computational cost of reconstruction and the time of data acquisition. In this work, we develop a novel multi-view free-space TD-DOT system utilizing an advanced single photon avalanche diode (SPAD) array. Our system utilizes a programmable scanning galvanometer to perform both surface extraction and optical tomography, enabling imaging of irregularly shaped objects. The surface extraction feature allows for more accurate modeling of the object's boundary, leading to improved reconstruction quality. To address the challenges associated with long acquisition times and high reconstruction cost, we propose a projection view optimization strategy that evaluates the independence of measurements from different projection views. The selected small set of projection views can provide sufficient measurement information without sacrificing reconstruction quality, thereby lowering the computational load and increasing the imaging speed. Through rigorous simulations and phantom experiments, we demonstrate that our system achieves superior imaging performance, particularly in complex-shaped objects, while the projection angle optimization algorithm ensures efficient data acquisition. This optimized view TD-DOT system holds potential for real-time monitoring of dynamic biological processes, such as hemodynamics.

[TP-59] PIBM2024-0819-14

Development of Betulinic Acid-Conjugated Axially Substituted Silicon Phthalocyanine Nanoparticles for Imaging-Guided Photodynamic Therapy in Breast Cancer Treatment

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Abstract: Photodynamic therapy (PDT) is a vital approach in cancer treatment, leveraging the unique properties of photosensitizers. Silicon phthalocyanine, as a second-generation photosensitizer, is known for its exceptional photophysical properties and biocompatibility, while betulinic acid is recognized for its potent anticancer activity. In this study, betulinic acid was employed as a ligand to substitute at the axial position of silicon phthalocyanine, resulting in the synthesis of Betulinic Acid-Axially Substituted Silicon Phthalocyanine (Bai-SiPc). The compound was further encapsulated using TPA-mPEG (triphenylamine polyethylene glycol) to form TPA-mPEG@Bai-SiPc nanoparticles. The structure of the resulting complex was characterized by ^{1}H NMR, FT-IR, and MALDI-TOF-MS. The photodynamic therapy efficacy of TPA-mPEG@Bai-SiPc was evaluated using the MCF-7 breast cancer cell line as the model. The findings indicate that TPA-mPEG@Bai-SiPc exhibits excellent biocompatibility and strong phototoxicity, establishing it as a highly effective photosensitizer with superior PDT performance against breast cancer.

[TP-60] PIBM2024-0819-16

Segmentation and reconstruction of renal tubule in mesoscopic mouse kidney images

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Abstract: The kidney is an important organ for excreting metabolic wastes and maintaining the stability of the internal environment in the body. The renal tubule is an essential structure for the nephron with reabsorption and excretion. Structural changes in the renal tubules can lead to kidney dysfunction and thus cause renal diseases. With the development of imaging technology, mesoscopic optical imaging can obtain kidney images at cell resolution. It is significant to reconstruct the three-dimensional (3D) morphology of renal tubules from the image to understand renal function and explore the pathogenesis of renal diseases. However, the large volume of high-resolution image data and the extensive spatial distribution of the renal tubule throughout the kidney present significant challenges for 3D reconstruction. To address this, we propose a deep learning-based method for renal tubule reconstruction. First, we propose a deep learning-based method for renal tubule reconstruction. First, we imaged mouse kidneys using High-Definition Fluorescent Micro-Optical Sectioning Tomography (HD-fMOST) to obtain kidney images at cellular resolution. We then employed a U-Net model to segment the renal tubules in two-dimensional (2D) kidney images, producing binary segmentation results. Finally, we performed the connected domain analysis of the segmentation results in 3D space and reconstructed the 3D morphology of all renal tubules. Our method demonstrates efficient and accurate reconstruction of renal tubules in mesoscopic kidney images

[TP-61] PIBM2024-0819-21

Multiphoton microscopy for visualization of fibrous meningioma

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Abstract: Extracellular matrix (ECM) proteins play a key role in the growth and biomechanical properties of fibrous meningiomas. In particular, the growth and invasive behavior of tumor cells may be impacted by the distribution and accumulation of collagen. In this study, we used label-free multiphoton microscopy (MPM) imaging combined with spectroscopic to analysis the distribution of collagen around tumor cells in fibrous meningiomas. The results demonstrate that the MPM imaging technique not only allows for the visualization of the fibrous network structure formed by collagen around tumor cells, but also able to quantitatively assess the collagen content. This finding provides new insights into the role of collagen in fibrous meningiomas and further lays a scientific foundation for the development of personalized treatment strategies and novel diagnostic and therapeutic targets.

[TP-62] PIBM2024-0819-22

Ultrasensitive near infrared microscopic imaging based on photon-number-resolved SNSPD

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Abstract: The scattering and absorption characteristics of biological tissues limit the penetration depth of high-resolution optical microscopy imaging of mammals in vivo. Compared to the visible light and the first near-infrared (NIR-I) window, the second near-infrared window (NIR-II, wavelengths >1000 nm) is an effective approach to reducing light scattering in biological tissues and increasing imaging depth in optical microscopic imaging. Superconducting nanowire single-photon detectors (SNSPD) have the characteristics of high sensitivity, low dark counts, and low timing jitter. In this paper, we propose a NIR-II microscopy imaging system based on a photon-number-resolved SNSPD, which has the advantages of higher photon counting rate and up to 6 photon number resolution compared to conventional SNSPD. SNSPD covers a detection range from 400 to 2400 nm and achieves a peak quantum efficiency of approximately 90% at 1550 nm. Experimentally, we analyze and discuss the imaging results in the samples with different incident wavelengths, which demonstrated a larger dynamic range and higher sensitivity in our system. Our results suggest that the system can be applied to biomedical imaging applications or quantum optics applications.

[TP-63] PIBM2024-0820-3

Exploring Organellar Dynamics and Interactions with SZ-SiPcI2: A Two-Photon Photodynamic Synergistic Fluorescent Probe

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Abstract: Silicon phthalocyanine complexes, with their additional two axial bonds, have gained significant attention in recent years as second-generation photosensitizers for photodynamic therapy. In this study, laser scanning confocal microscopy was employed to evaluate the intracellular distribution and cytotoxic effects of SZ-SiPcI2 (methylthiazole axially substituted silicon phthalocyanine) in BxPC-3 (Biopsy xenograft of Pancreatic Carcinomaline-3). The research focused on the time-dependent cellular uptake of SZ-SiPcI2 and its interactions with various subcellular organelles. The subcellular localization of SZ-SiPcI2 was analyzed alongside organelle-specific fluorescence probes, and alterations in mitochondrial morphology and membrane potential were closely monitored. The preliminary findings elucidate the cytotoxic mechanisms of this silicon phthalocyanine complex, highlighting its good biocompatibility. This study not only offers new strategies for the effective eradication of cancer cells but also provides a robust foundation for future research aimed at monitoring bioactive molecules associated with subcellular organelles.

[TP-64] PIBM2024-0820-4

Virtual Histopathology through Optical Coherence Tomography

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Abstract: Histopathological examination of tissue sections plays a crucial role in clinical diagnosis, providing information on cell morphology, tissue structure, and abnormal changes. Nowadays, histopathology procedure involves complicated protocols including tissue dehydration, embedding, ultra-thin microtome slicing, slice mounting and staining, as well as manual examination under a microscope. Such procedure is carried out in hospital by multiple experienced pathologists and can take several days before the final results came out. As a consequence , histopathology has been one of the bottlenecks of diagnose and a huge burden to pathologists. Therefore, advancing automated histopathology technologies can significantly improve efficiency, relieve burden, making it essential for personalized healthcare. This project aims to develop a high-throughput, 3D histopathological examination technology by integrating novel optical coherence tomography imaging routine with AI-driven virtual staining tools to provide traditional Hematoxylin and Eosin (H&E) equavalent digital histopathology. This approach will revolutionize traditional histopathology, enabling faster, more precise, and reliable tissue analysis. By replicating traditional H&E staining through AI, our project will bridge advanced

imaging and clinical application, improving diagnostic interpretability and patient outcomes, and setting a new standard in pathological diagnostics.

Building on past collaborations, our multidisciplinary team of experts in optical imaging, AI, and pathology is advancing a new research initiative. The Chinese team will develop a serial vibratome sectioning system integrated with Optical Coherence Tomography (OCT) to capture high-resolution 3D images of brain and breast tissues. On the other hand, the Turkish partners will create a generative adversarial network-based algorithm to virtually stain these images, converting them into digitally stained H&E equivalents. This virtual staining tool will be deployed in both clinical and research settings, with training and support provided to pathologists. In surgical environments, the tool will enhance the speed and accuracy of intraoperative tissue evaluation, improving surgical decision-making.

[TP-65] PIBM2024-0820-17

Assessment of CO_2 Fractional Laser Treatment Efficacy in Localized Scleroderma Using Optical Coherence Elastography

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Abstract: Localized scleroderma is a chronic autoimmune disease characterized by skin thickening and fibrosis, severely impacting patients' quality of life. In advanced cases, it can lead to deformities, resulting in significant functional impairments. While CO_2 fractional laser therapy has shown promise in alleviating these symptoms by promoting collagen regeneration and remodeling, the challenge lies in accurately assessing its efficacy. Traditional methods for evaluating treatment outcomes are often hampered by subjectivity and complexity, creating a need for more reliable alternatives.

To overcome these challenges, this study employs Optical Coherence Elastography (OCE) to provide a real-time, non-invasive evaluation of the biomechanical changes in skin before and after treatment. OCE offers high-resolution, quantitative data that addresses the limitations of conventional assessment methods. Six patients with localized scleroderma were treated with CO_2 fractional laser therapy and monitored over a five-month period. Assessments were conducted at baseline and at one, two, three, and five months post-treatment. Results showed significant improvements in skin texture and reduced fibrosis, as indicated by increased elasticity, decreased stiffness, and more organized collagen fibers, as captured by OCE. Importantly, OCE was particularly effective during the one, two, and three-month follow-up assessments, where it detected subtle biomechanical changes that were not apparent through conventional clinical observations. This early detection capability facilitated timely adjustments to treatment protocols, thereby optimizing therapeutic outcomes.

In conclusion, OCE proves to be a potential tool for objectively evaluating the efficacy of CO_2 fractional laser treatment in localized scleroderma. Its ability to deliver precise, quantitative data supports the development of individualized treatment strategies. Moreover, the non-invasive, real-time imaging capabilities of OCE enhance

patient comfort and satisfaction, paving the way for its broader application in both research and clinical settings for the management of localized scleroderma.

[TP-66] PIBM2024-0821-2

Multi-Modality Laparoscopic System Design and Application

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Abstract. Laparoscopic system is widely used in minimal invasive surgery providing visualization to surgeons. The state of art laparoscopic system allows for white light and ICG fluorescence imaging which is belong to optical imaging. Aside from that, we developed a non-invasive multi-modality laparoscopic system enables additional tissue functional imaging such as oxygen saturation and blood flow imaging in one system.

The oxygen saturation imaging measures tissue oxygen saturation (StO2) of the tissue in abdomen during surgery. This modality has potential for discriminating between tumors and their adherent substances. In additional, the StO2 imaging is an indicator to monitor the StO2 changing during resection surgery. The laser speckle contrast imaging (LSCI) is a tool to monitor blood flow distribution and indicates the microcirculation perfusion of the tissue. The two additional functional image modalities are label free and use infrared laser permits deep penetration of the tissue. Overall, the four image modalities are complementary to each other and offers more clinical indicators which improves the confidences of diagnosis without changing its usability.

The system uses four CMOS image sensor for image acquisition. A FPGA+ARM architecture is introduced for high resolution image processing up to 1920*1080 in real time. Specifically, the FPGA is used to calculate the StO2 imaging and LSCI blood flow imaging based on four channels. The multi wavelength light source is designate to provide the illumination per each modality.

At last, the animal experiments and clinical trial are performed in order to verify its functionality and performance. We designed the animal test protocol to showcase the monitoring of oxygen saturation by vascular clamp during gastrointestinal surgery. We also carried out the clinical study in human lung tumor segmentectomy by laparoscope. The test results showcase that the multi-modality imaging bring more clinical benefits and improves the accuracy of diagnosis and precision.

[TP-67] PIBM2024-0927-2

Motion artifact correction using normalized cross-correlation of cropped B-scans

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Abstract: Optical coherence tomography angiography (OCTA) images are susceptible to motion artifacts caused by slightly jitter, which was derived mainly from the heartbeat and respiration of live samples. These motion artifacts lead to a greater degree of decorrelation in static tissues compared to vascular regions, while the unwanted strip artifacts are presented in *en-face* images of OCTA. In this paper, we propose an additional gradient analysis for surface identification as part of the pre-processing stage using conventional normalized cross-correlation correction algorithm. Subsequently, the upper and lower surfaces of OCT structures were utilized to extract B-scans containing only the static tissue and blood vessel region. The results demonstrated that the normalized cross-correlation of cropped B-scans presents better motion artifact correction performance than the normalized cross-correlation of successive entire B-scans.

[TP-68] PIBM2024-0929-1

High resolution characterization by air-coupled photoacoustic tomography for femtosecond laser filament

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Abstract: Femtosecond laser filaments have significant potential in applications such as remote sensing of atmospheric components, guided discharge, and induced water vapor condensation. However, due to their small diameter (on the order of hundreds of micrometers) and high internal intensity, current measurement methods struggle with limited sensitivity, resolution, and complexity, making it challenging to quantitatively and promptly assess the internal structure of the filaments. During filament formation, some pulse energy is deposited as heat, generating ultrasound signals that carry rich internal information. We propose an Air-Coupled Photoacoustic Tomography (APAT) technique, which considers finite aperture size conditions. Theoretical derivation and simulations confirm that APAT can achieve high-resolution imaging over the mean free path in air and accurately quantify the changes in image quality due to finite aperture size. Experimental results with tungsten wire samples demonstrate that APAT's resolution capability is three times greater than that of water-coupled PAT. APAT offers a high-resolution, non-destructive imaging strategy under dry conditions.

[TP-69] PIBM2024-0930-1

In vivo Research of the Blood Flow in a Mouse Pressure Ulcer Model by Using Laser Speckle Contrast Imaging

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Abstract: Pressure ulcer is a common condition for patients who are bedridden or have limited mobility. When the skin and underlying tissues undergo repeated ischemia and reperfusion due to compression, it leads to inflammation and ulcer formation. Although traditional immunobiochemical methods can detect pathological characteristics, they lack the capability for real-time and accurate detection of blood flow in pressure ulcer sites. In this study, two models of pressure ulcer on mouse ears were established, and the blood flow after pressure ulcers was monitored using a laser speckle contrast imaging (LSCI) system. Maps of blood flow revealed that after a single 1.5-hour pressure ulcer on the mouse ear, the blood flow perfusion at the compressed area gradually recovered over time, and essentially returned to normal by the 7th day. Conversely, with continuous daily pressure ulcers for 1.5 hours, the compressed area showed almost no perfusion by the 4th day, and the ulceration was fully formed by the 7th day. Compared to white light imaging, LSCI offers more precise monitoring of blood flow at pressure ulcer sites. The research solves the problem of dynamic functional monitoring of the blood flow velocity changes at spatial resolution. It provides a new technology for dynamic assessment of pressure ulcers, and offers a new method for the care and treatment of clinical patients.

[TP-70] PIBM2024-1009-1

Targeted near-infrared imaging of tissue injury

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Abstract: Timely and accurate monitoring of biomarkers in tissue damage is essential for assessing therapeutic efficacy. Optical imaging technologies often face limitations in sensitivity, specificity, and tissue penetration depth, hindering detailed observation of tissue injury and repair processes. miRFP670nano3 is a new near-infrared fluorescent protein with high photostability, resistance to acidic and alkali environment and tissue penetration. Despite its favorable properties, miRFP670nano3 lacks inherent specificity for imaging tissue damage. During tissue injury, phosphatidylserine on the inner leaflet of the cell membrane is exposed to the outer membrane as a marker of tissue damage. Lactadherin is a calcium-independent phosphatidylserine-binding protein expressed during lactation in the mammary glands. We previously determined the crystal structure of phosphatidylserine bound by a binding protein lactadherin C2 domain, where its C2 domain binds to phosphatidylserine with high affinity (Kd of ~3.3 nM). The C2 domain of lactadherin can bind specifically to phosphatidylserine on the surface of damaged tissue, providing a new approach for tissue injury targeting. This study aims to explore the application of the lactadherin C2 domain-miRFP670nano3 fusion protein for in vivo imaging of skin tissue injury. We prepared the lactadherin C2 domain-miRFP670nano3 fusion protein and established a mouse skin injury model using an excisional wound method. Fluorescence imaging of the injured area was performed using the FMT 2500 fluorescence molecular tomography scanner. Our results revealed that the lactadherin C2 domain-miRFP670nano3 exhibited specific fluorescence signals in the in vivo mouse skin injury model, which gradually diminished alongside wound healing, potentially reflecting the clearance of phosphatidylserine by phagocytic cells during tissue damage

and repair. Furthermore, the high stability and pH tolerance of miRFP670nano3 facilitate prolonged observation. This study not only demonstrates the potential of the lactadherin C2 domain for targeting phosphatidylserine exposure at wound sites but also underscores the advantages of miRFP670nano3 for in vivo imaging.

[TP-71] PIBM2024-1011-1

Study on the bone thermal injury evaluation in microwave ablation by combining CT and near-infrared parameters

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Abstract: The ablation technique is very important in the interventional treatment of bone tumors. In order to explore the real-time thermal damage effect of bone tissue during surgery, in our previous studies, the bone tissue thermal damage during microwave ablation was studied based on near-infrared spectroscopy. However, how to quantify the thermal damage is a problem. In this paper, the combining near-infrared parameters, CT values, and thermal injury factors of bone tissue during microwave ablation was proposed, and the bone tissue thermal injury evaluation model was established. First, pig bone was used as the experimental model and the microwave ablation experimental plan was developed to measure the near-infrared spectra of bone tissue before and after the experiment. Then the characteristic factors were analyzed. Second, the bone tissue in the experimental area were subjected to CT detection, and the correlation between CT values and characteristic factors were studied. Finally, based on the correlation study, bone tissue thermal injury factors were designed, and the evaluation model was constructed based on CT values, thermal injury factors, and near-infrared characteristic factors. The results showed that both CT values and characteristic factors were significantly related to the bone tissue thermal damage. There was a linear relationship between CT values and near-infrared characteristic factors. The results could be used for quantitative grading of bone tissue thermal injury in microwave ablation. The evaluation model provides important value for the development of microwave ablation bone tissue treatment systems.

[TP-72] PIBM2024-1015-2

Study on Surface Enhanced Raman Spectroscopy of Kidney Cancer based on Ag NC Enhanced Substrate

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Abstract: Surface enhanced Raman spectroscopy (SERS) has been widely used as a sensitive sensing technology in the medical field because of its unique molecular fingerprint information. In this paper, silver nanospheres (Ag NPs) and silver nano-cube (Ag NC) nanoparticles with different morphologies were constructed based on silver nanomaterials for the purpose of early screening of kidney cancer. By analyzing

the SERS characteristics of nanoparticles, it was found that the enhancement effect of Ag NC was greater than that of Ag NPs. SERS detection was performed on the urine of 30 patients with kidney cancer and 30 normal subjects. By analyzing the spectral differences between cancer patients and normal people, the cancer group and normal people were preliminarily distinguished. We analyzed the measured spectral data. The analysis methods mainly included principal component analysis (PCA) and linear discriminant analysis (LDA) diagnostic algorithms, as well as recursive weighted partial least squares (PLS) and support vector machine (SVM) algorithms. The comparison of the two classification algorithms shows that the classification accuracy of PLS-SVM is 99.13%, sensitivity was 98.67%, specificity was 100%, and AUC value was 1. The classification effect was much higher than PCA-LDA. The results of this exploratory research show that the combination of Ag NC substrate and PLS-SVM algorithm has greater potential in the pre diagnosis and screening of Kidney cancer.

[TP-73] PIBM2024-1015-4

Activatable chemiluminescence probe based on four-arm PEG-conjugated-pyropheophorbide-a for in vivo autofluorescence-free imaging of peroxynitrite

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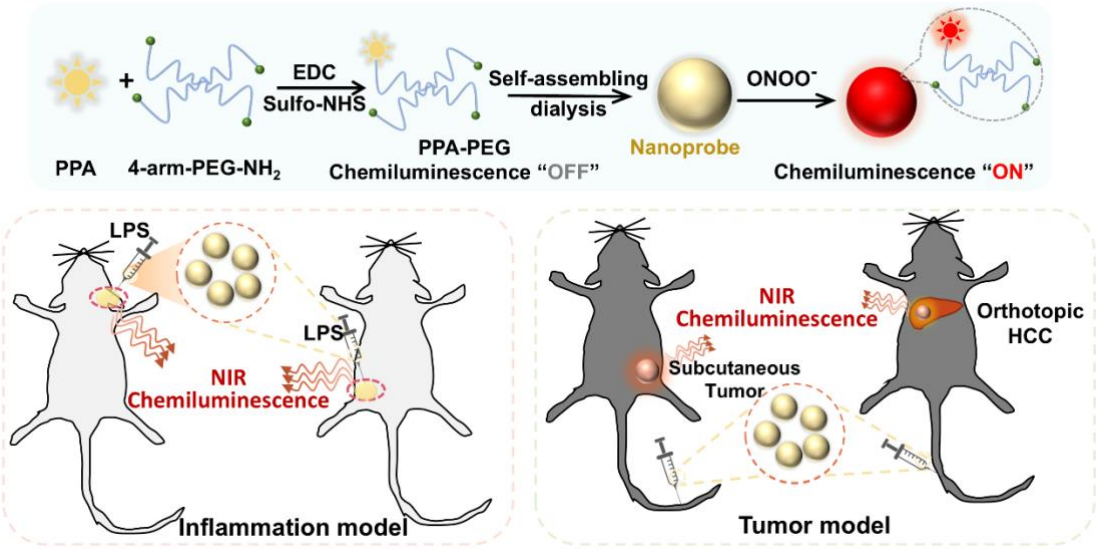
Abstract: Peroxynitrite ($ONOO^-$) is a highly reactive nitrogen species that plays pivotal roles in cell signal transduction and physiological or pathological progresses. However, commonly used $ONOO^-$ optical imaging probes are still hampered by high background/autofluorescence (fluorescence probe), short emission wavelength, or poor selectivity in the case of chemiluminescence. Herein, we report a facile method to prepare an activatable chemiluminescence probe (PPA-PEG) with good biocompatibility and functionality for *in vivo* autofluorescence-free imaging of $ONOO^-$. The PPA-PEG consists of pyropheophorbide-a (PPA), a typical deep red photosensitizer that acts as both the recognition and signaling element, and 4-arm poly(ethylene glycol) (4-arm PEG), which improves the biosafety and water solubility of probe. These components can self-assemble into nanoparticles (namely PPA-PEG nanoprobe) in aqueous solution. The PPA-PEG nanoprobe showed an ultra-low chemiluminescence signal before interacting with $ONOO^-$, but exhibited good selectivity, high sensitivity and a fast response toward $ONOO^-$. The PPA-PEG was successfully applied to image cellular $ONOO^-$ changes, as well as the endogenous $ONOO^-$ changes in inflammation models and subcutaneous or orthotopic hepatocellular carcinoma (HCC) tumors models in living mice. *In vitro* and *in vivo* studies verified the good detection and imaging capabilities of PPA-PEG for peroxynitrite, demonstrating suitable tissue penetration and a high signal-to-background ratio (SBR). Thus, our nanoprobe can serve as a valuable activatable chemiluminescence imaging tool for studying important peroxynitrite related chemical and biological applications.



[TP-74] PIBM2024-1015-7

Deep learning-based De-scattering in Two-photon Fluorescence Microscopy

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Abstract: Two-photon-excited fluorescence (TPEF) microscopy excels in in vivo deep tissue imaging, making it a vital tool for exploring biological tissues. However, deep layer imaging faces challenges from biological scattering, impacting image quality. To address this, we develop a deep learning-based de-scattering method for two-photon excitation fluorescence imaging (DeS-TPEF). This method employs a multi-attention model that focuses on the reconstruction target. It also utilizes a multi-component optimization strategy, guided by the minimum-cross-entropy threshold segmentation with Dice similarity coefficient (MCE_DSC) loss function, to minimize the false positives in the reconstruction process. To train a network capable of de-scattering images affected by real-world high scattering, we designed a simulated scattering model. This model can degrade images from conditions of shallow depth, no/low scattering, and high signal-to-noise ratio to those representing deep depth, high scattering, and low signal-to-noise ratio. Our quantitative validation involved static scattering fluorescent beads and vascular systems under biological dynamic scattering. The results showed significant improvements in NRMSE, PSNR, and SSIM compared to the original data. We demonstrate our method in real-world experimental imaging studies, including in vivo imaging of the cerebrovascular system within mice at depths of up to 850 μm.

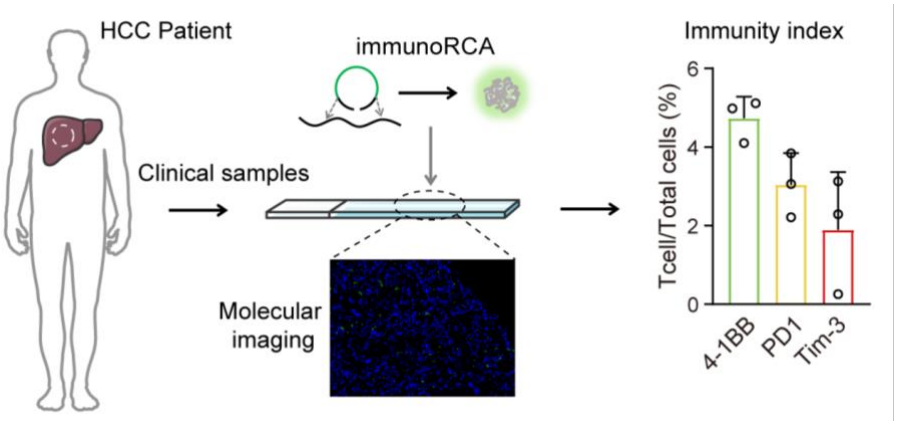

Fig. 1 Schematic diagram of single-cell in situ imaging of immune status for TILs by immunoRCA.

[TP-75] PIBM2024-0726-1

A non-invasive method for evaluating changes in subcutaneous fat layer of mice induced by diacylglycerol and their compositions

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Abstract: Optical coherence tomography (OCT) enables the non-invasive acquisition of highresolution three-dimensional cross-sectional images at a micrometer scale for (epi-)dermis layer and subcutaneous fat layer of mouse skin. In this paper, we present a method to predict individual weight loss induced bydiacylglycerol and their compositions based on a deep-learning algorithm for the subcutaneous fat layer of mouse skin in OCT image using convolutional neural network (CNN). Our results demonstrate that individual weight loss is related to the subcutaneious fat layer of mice. Then diacylglycerol, composition containing diacylglycerol and xylooligosaccharide, and composition containing diacylglycerol, medium chain triglycerides, medium- and long-chain triacylglycerol oil, and xylooligosaccharide have a small positive effect on weight loss, since that the subcutaneious fat layer become thinning. The potential suggets the subcutaneous fat layer of mice based on OCT combined with CNN could be used as a method to evaluate the weight loss induced by diacylglycerol and their compositions.