组织光学成像及其生物医学应用

Tissue Optical Imaging — Principles and Biomedical Applications

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内容提要

1、物理基础和实现方式

2、工作原理与测量模式

3、生物医学应用系统

4、方法与技术展望

传统光学

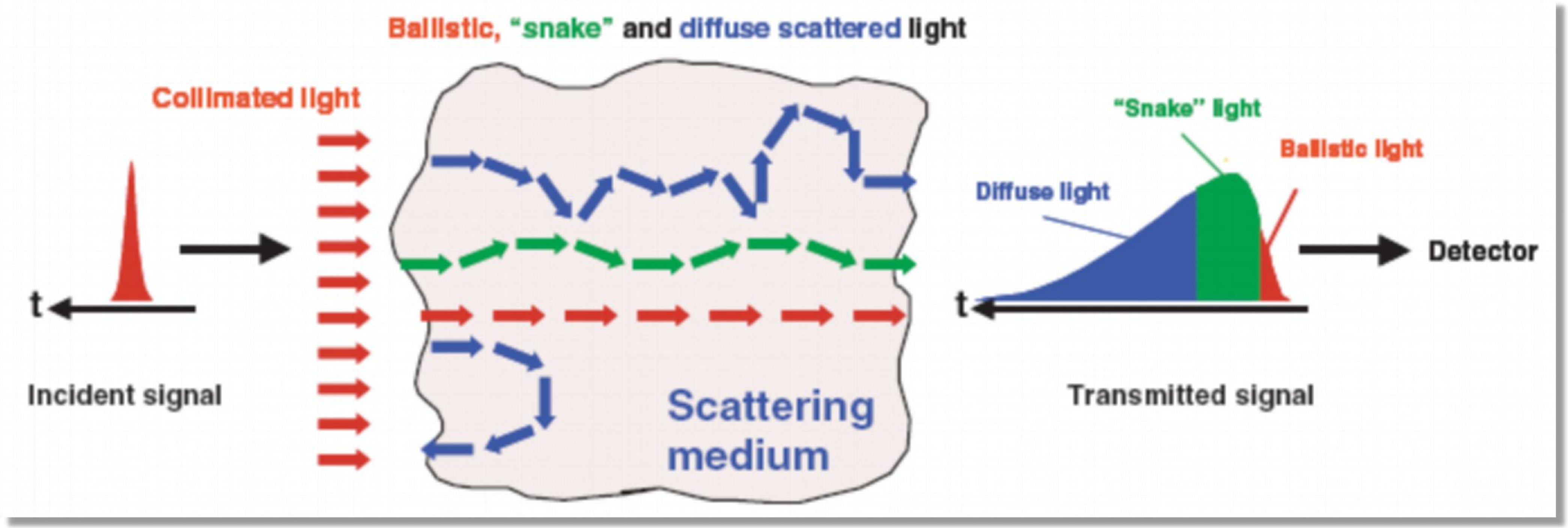
Coherent Light Imaging

- Depth: 1-3 mm
- Spatial Resolution : 1-15 μm

组织光学

Diffuse Light Imaging

- Depth: 5-10 cm
- Spatial Resolution: 1-5 mm

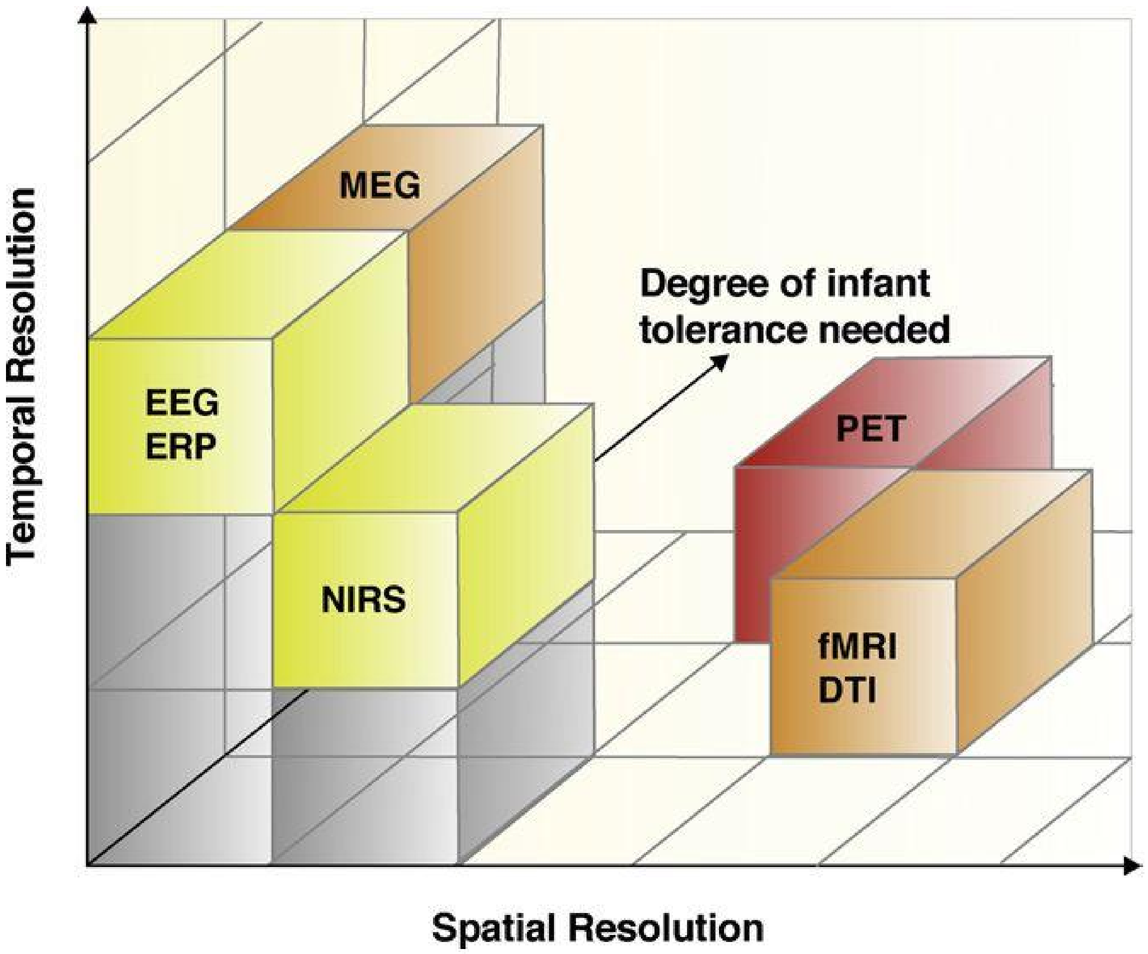


Established Medical Functional Imaging Modalities

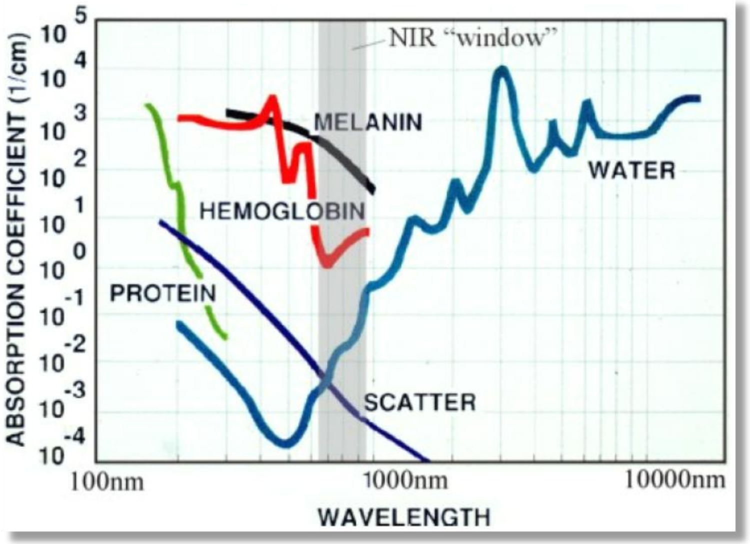
- **fMRI:** high spatial-resolution but low temporal-resolution, only total hemoglobin (THb), and unmovable.
- **PET:** high-sensitivity, radiation emitter, bulky, and expensive.
- **EEG/MEG:** high temporal-resolution, low spatial-resolution, and Low electromagnetic resistance

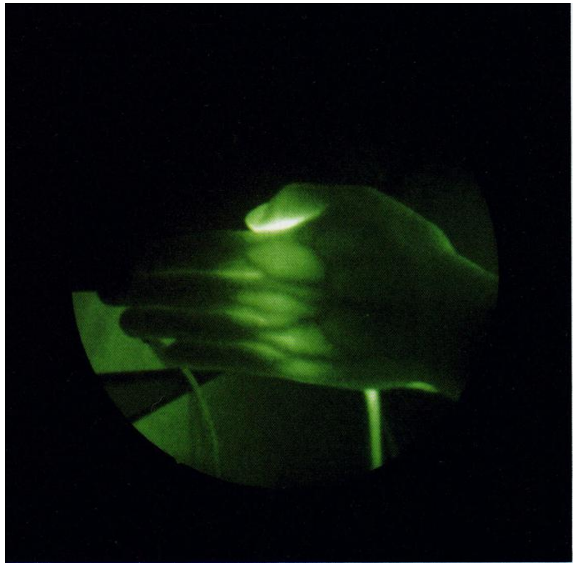
Optical Imaging (NIRS)

- ✓ Completely non-invasive;
- ✓ Higher temporal-resolution with reasonable spatial-resolution;
- ✓ Direct measurement of oxy- and deoxy-hemoglobin concentrations;
- ✓ Portable & wearable.

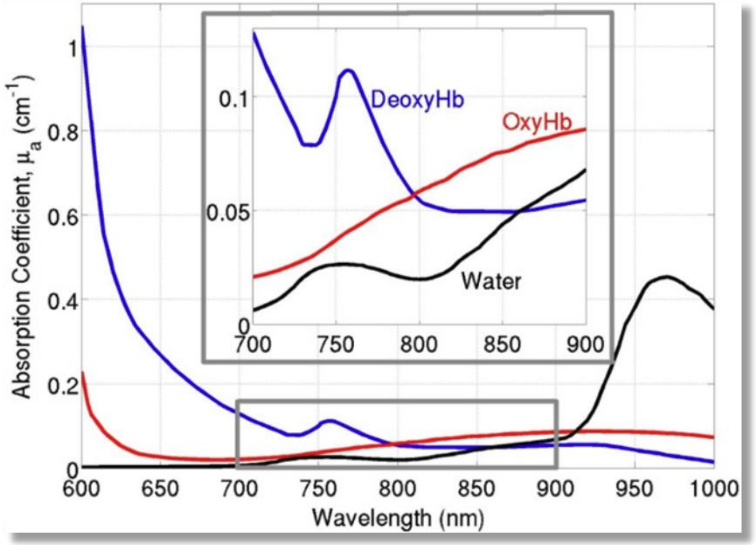


① 窗口效应





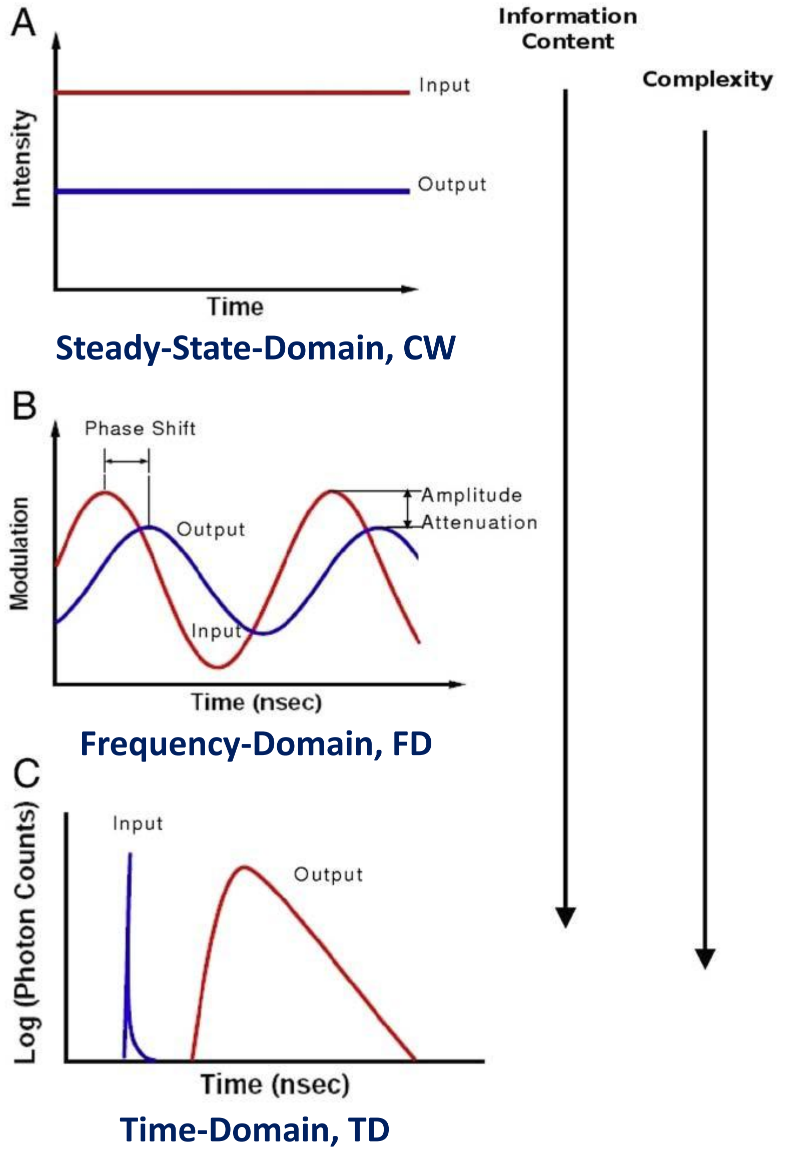
② 色差效应



Hemoglobin Concentrations:

$$
\begin{cases}
[Hb] = \dfrac{\varepsilon_{HbO_2}^{\lambda_2} \cdot \mu_a^{\lambda_1} - \varepsilon_{HbO_2}^{\lambda_1} \cdot \mu_a^{\lambda_2}}{\varepsilon_{HbO_2}^{\lambda_2} \cdot \varepsilon_{Hb}^{\lambda_1} - \varepsilon_{HbO_2}^{\lambda_1} \cdot \varepsilon_{Hb}^{\lambda_2}} \\
[HbO_2] = \dfrac{\varepsilon_{Hb}^{\lambda_1} \cdot \mu_a^{\lambda_2} - \varepsilon_{Hb}^{\lambda_2} \cdot \mu_a^{\lambda_1}}{\varepsilon_{HbO_2}^{\lambda_2} \cdot \varepsilon_{Hb}^{\lambda_1} - \varepsilon_{HbO_2}^{\lambda_1} \cdot \varepsilon_{Hb}^{\lambda_2}}
\end{cases}
$$

③ 测量模式

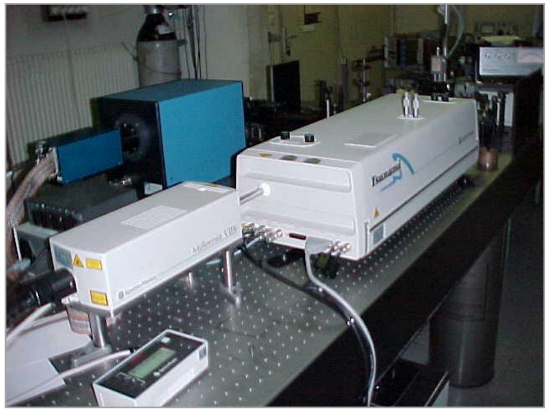


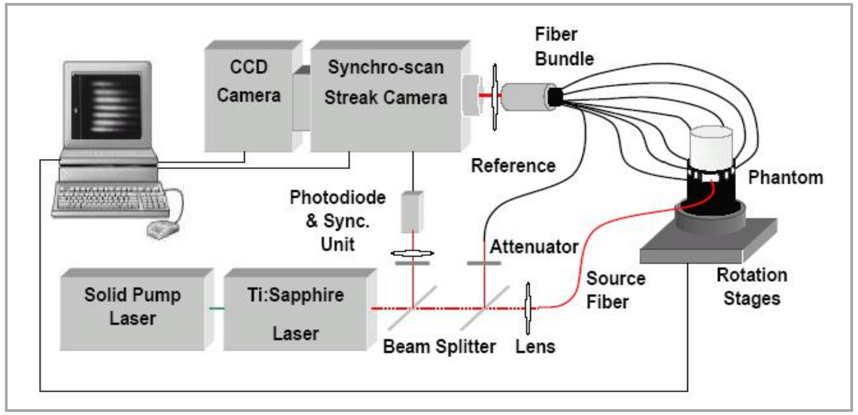
Phys. Med. Biol. 2003; *Rep. Prog. Phys.* 2010; *J. Biomed. Opt.*, 2016; *Appl. Sci.* 2019; *Nature Photonics* 2019

时域测量技术

SC/ICCD/TCSPC

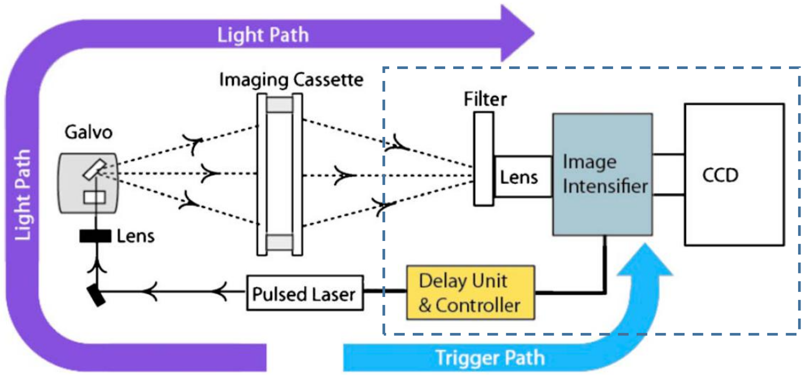
Streak Camera (SC)





High Temporal Resolution; Low Dynamic Range and SNR; Low Spatial Sampling; High Cost

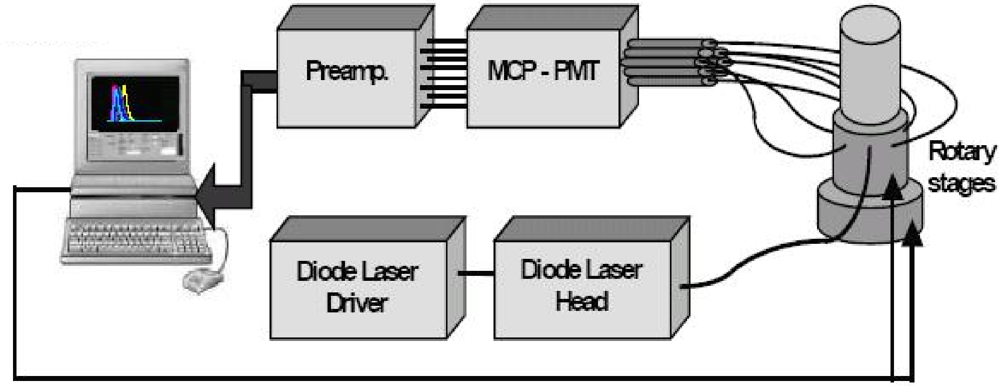
Time-gated ICCD



Reasonable Temporal Resolution; High Data Throughput; High Cost; Limited Dynamic Range and SNR

Time-correlated Single Photon Counting (TCSPC)

TOF Analyzer



Reasonable Temporal Resolution; High Dynamic Range and SNR; Limited Spatial Sampling; Relatively moderate cost

- 近红外组织光谱学
  (Functional Near-Infrared Spectroscopy, fNIRS)
- 光学拓扑成像
  (Optical Topography/Mapping, OT/M)
- 扩散光学层析*
  (Diffuse Optical Tomography, DOT)
- 荧光分子层析/扩散荧光层析*
  (Fluorescence Molecular Tomography, FMT/DFT)

*Computational Imaging Regime

组织光学成像

乳腺肿瘤诊断(Breast Tumor Diagnosis)

Differentiating between healthy and diseased tissues by measuring difference in optical properties of tissue

脑功能探测(Brain Function Analysis)

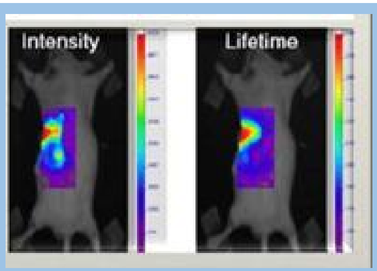
Separating changes in oxy- and deoxy-hemoglobin concentrations during physical and psychological excises

新生儿脑监护(Monitoring of Neonatal Brain)

Monitoring hemoglobin concentration and oxygenation to prevent perinatal hypoxic-ischemic brain injury

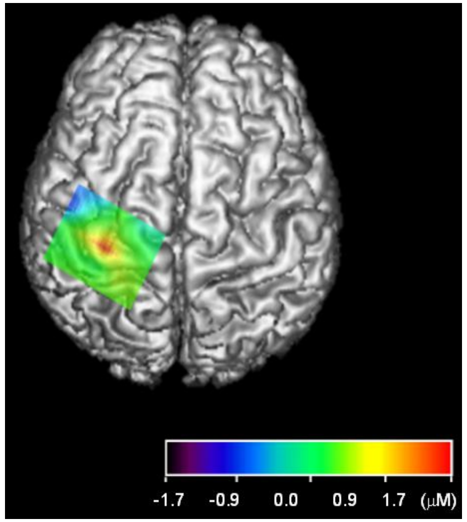
在体分子影像(*In-vivo* Molecule Imaging)

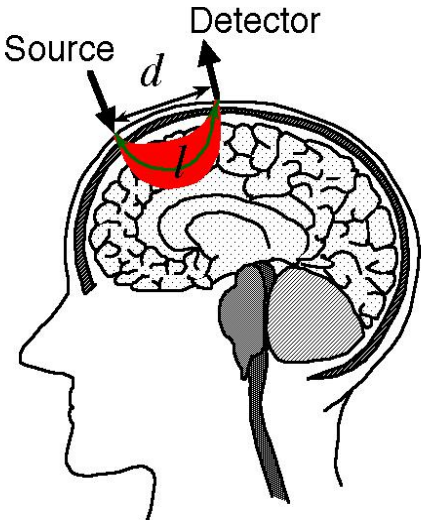
Volumetrically imaging molecular functions and events through fluorescent molecule-specific probe.



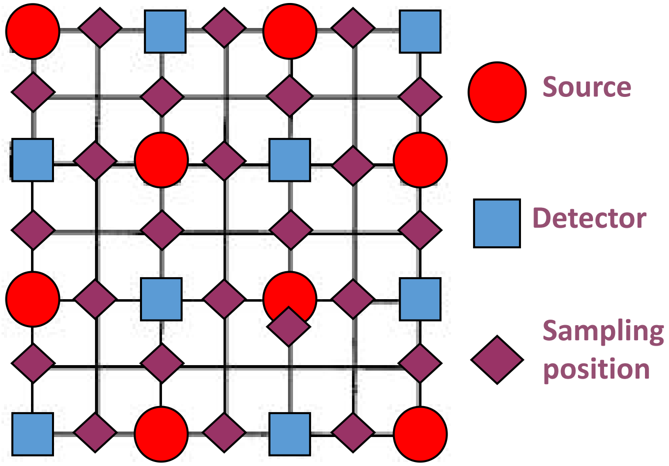
光学拓扑成像(Optical Mapping)

Measuring hemodynamics in a shallow (cerebral/muscel) areas under a source-detector array based on the Modified Lambert-Beer Law (MLBL)





l: Optical Pathlength



CW6 (美国)

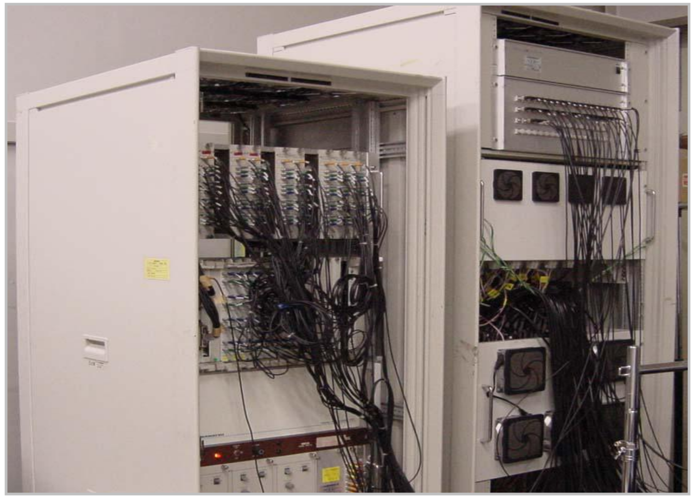
ETG4000 (日本)

OXYMON MkIII (荷兰)

$$\Delta A = \log\left(I_{task} / I_{rest}\right) = l\mu_a = l\varepsilon\Delta c$$

扩散光学层析(DOT)

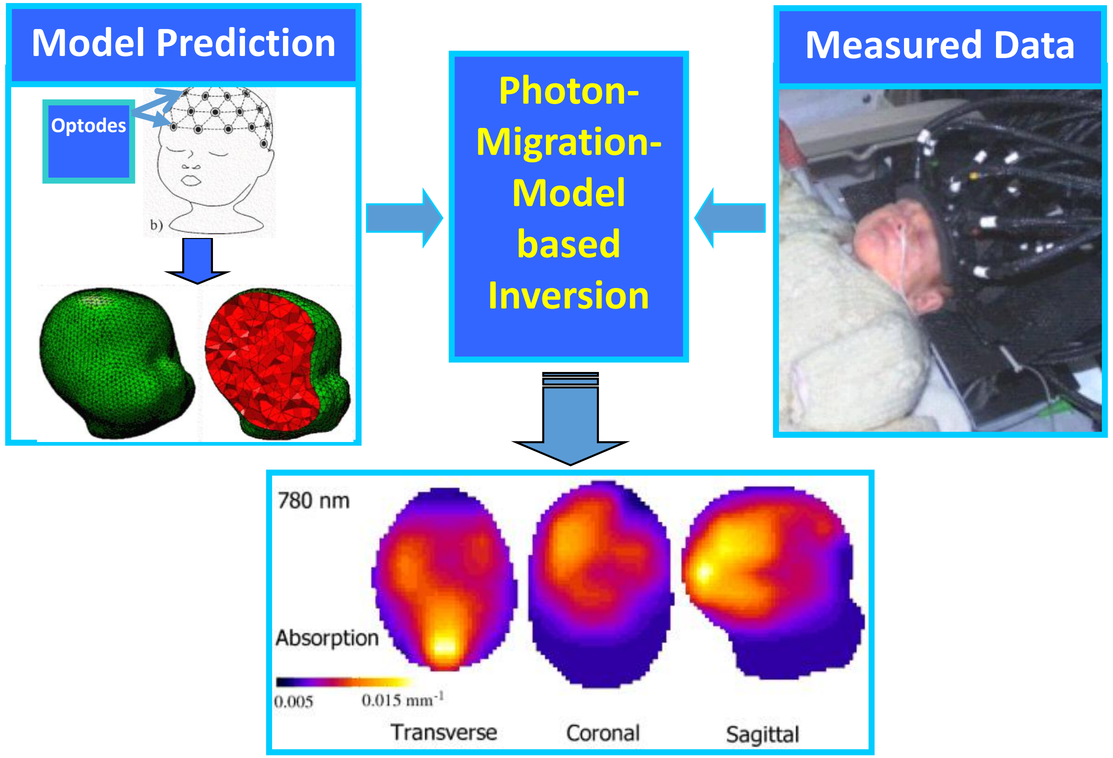
Probing hemodynamic status in a deep tissue by a discrete source-detector deployment on the boundary, assuming that an unique distribution of optical properties corresponds to the measurement set.



AIST系统 （日本）

MONSTIR系统 （英国）

基本原理



测量系统：多通道、高灵敏度、大动态；
光子输运模型：应用普适性和计算高效性；
图像反演理论：过程稳健性和结果唯一性。

Rev. Sic. Instrum. 1999; Rev. Sic. Instrum. 2000; Biomed Opt. Express 2013; Nature Photonics 2019.

辐射输运理论

随机模型

1. Random walk theory

2. Monte-Carlo method (accelerated by GPU)

- **Voxel-based**
- **Mesh-based**

确定模型

1. Radiative transfer equation (RTE)

2. **Photon diffusion equation (P_1)**

- **Finite-difference method (FDM)**
- **Finite-element method (FEM)**
- **Boundary-element method (BEM)**

3. High-order Spherical Harmonics (P_N)

4. Simplified Spherical Harmonics (SP_N)

***Opt. Lett.* 2013; *Opt. Express* 2015; *J. Biomed. Opt.* 2016; *Opt. Express* 2017; *Opt. Lett.* 2018.**

- **最大似然估计(MLE)**

$$\boldsymbol{\mu} = \arg\max\ p(\mathbf{M} \mid \boldsymbol{\mu})$$

  - **牛顿-拉夫逊非线性格式** $\mathbf{M} - \mathbf{F}(\boldsymbol{\mu}_k) = J(\boldsymbol{\mu}_k)(\boldsymbol{\mu}_{k+1} - \boldsymbol{\mu}_k)$
  - **直接非线性优化格式** $\boldsymbol{\mu} = \arg\min \|\mathbf{M} - \mathbf{F}(\boldsymbol{\mu})\|$

- **高斯-马尔科夫图像模型下的贝叶斯最大后验估计（MAP with Guassian-Markov Image Model）**

$$\boldsymbol{\mu} = \arg\max\ p(\boldsymbol{\mu} \mid \mathbf{M}) = \arg\max[\,p(\mathbf{M} \mid \boldsymbol{\mu})\,p(\boldsymbol{\mu})]$$

  - **坐标下降法**

- **基于深度学习的计算成像（Deep-learning based computational imaging）**

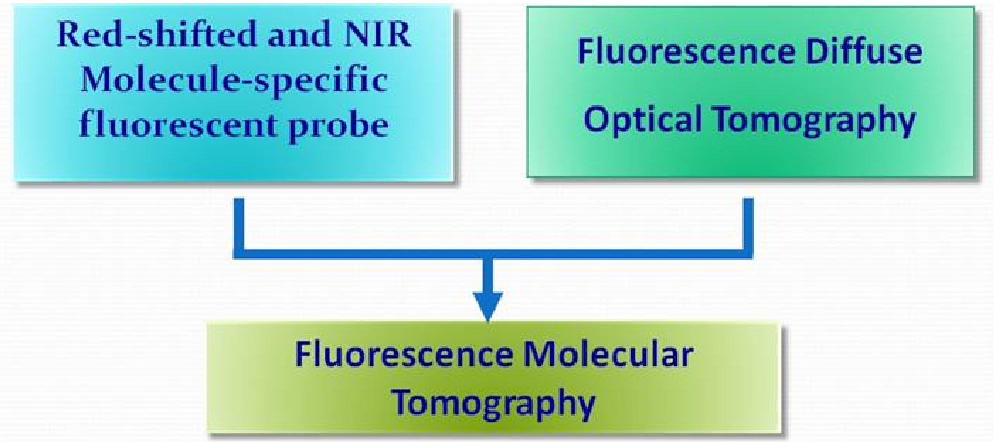
$$\boldsymbol{\mu} = \mathrm{NN}(\mathbf{M})$$

  - **黑箱法（End-to-End）**
  - **半黑箱法（Physics-informed）**

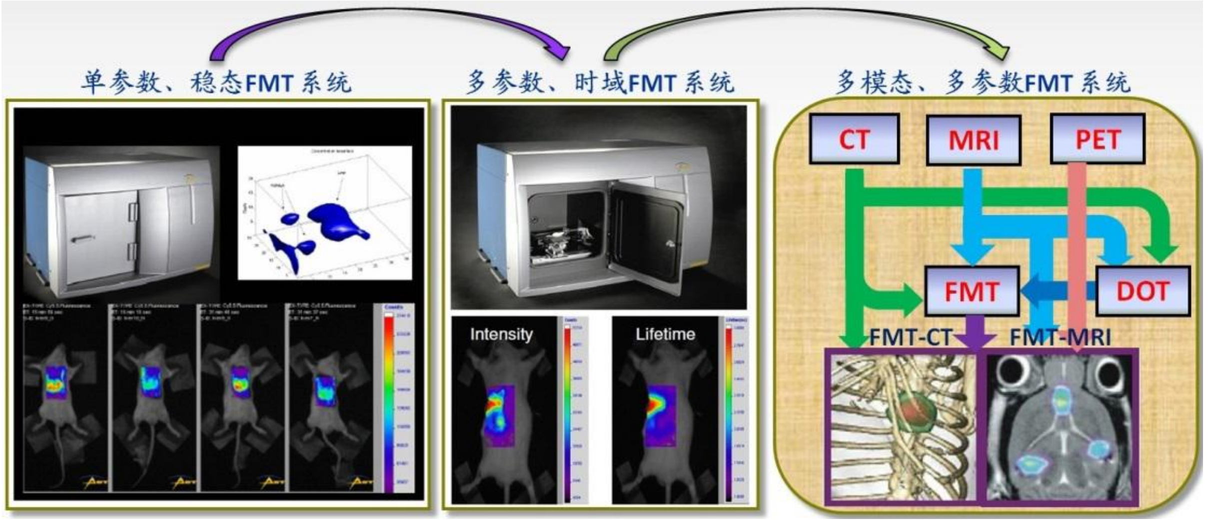
Appl. Opt. 2001, 2002, 2003, 2008, 2010; Phys. Med. Biol. 2004; J. Biomed Opt. 2007, 2012, 2016, Opt. Express 2006, 2008, 2017.

荧光分子层析

基本原理

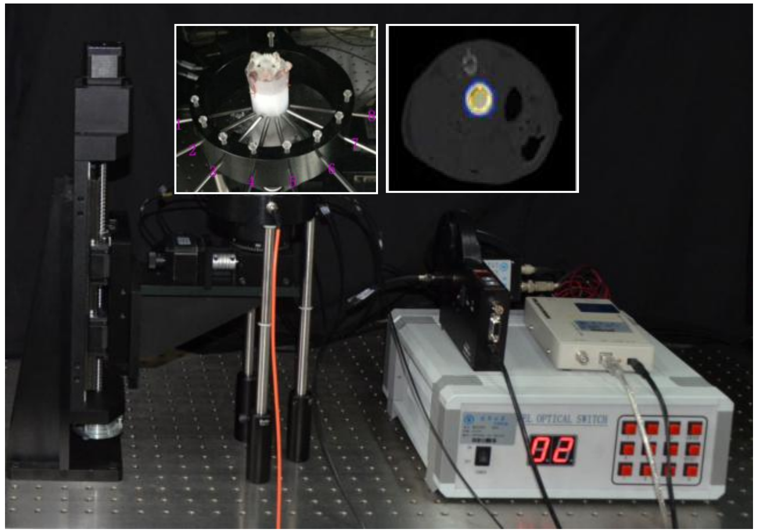


多模态、多参数方法

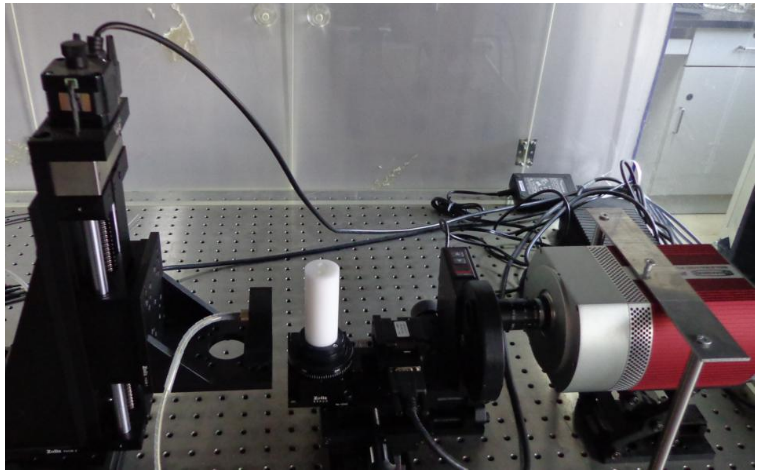


测量系统

光子计数



EM-CCD



Nature Med. 2002; *Opt. Lett.* 2013; *Appl. Opt.* 2010, 2012.

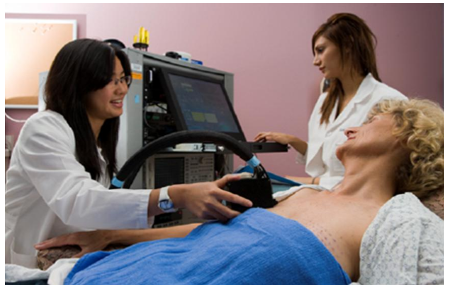
乳腺光学成像

压板扫描

Philips & GE

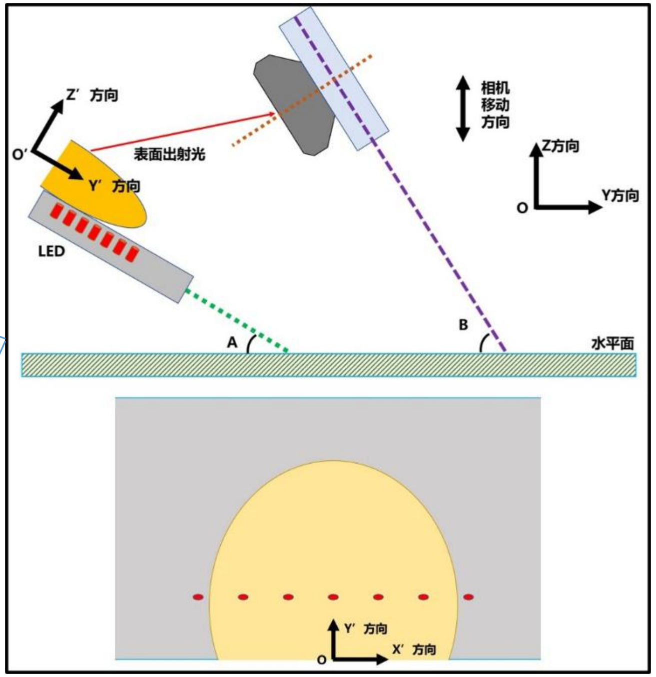
三维悬垂

手持反射式



动态式

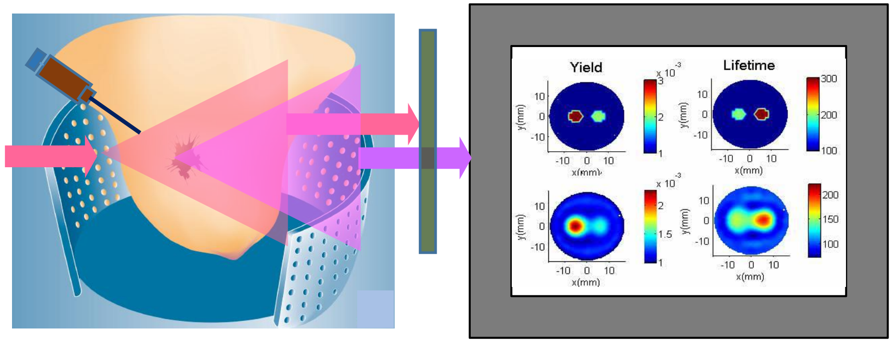
DOBI Medicine & TJU

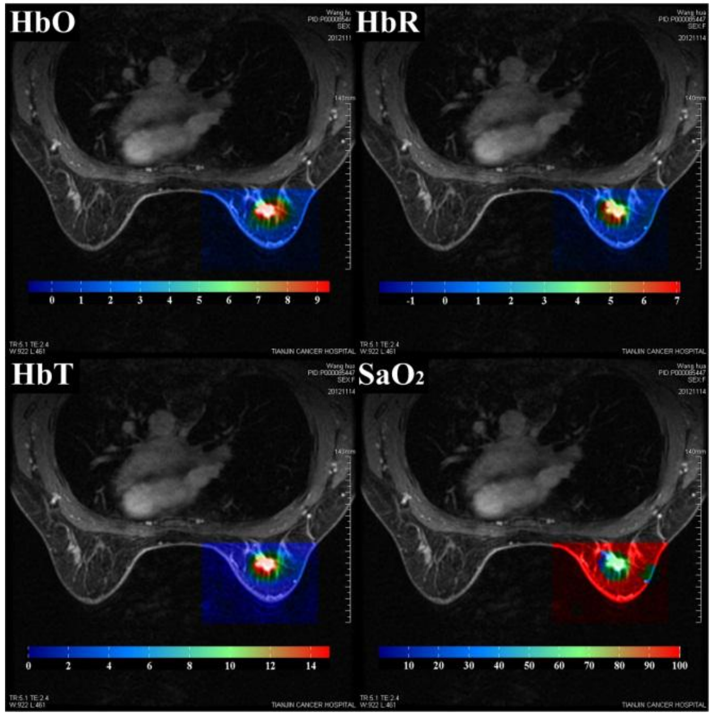


Phys. Med. Biol. 2005; J. Biomed. Opt. 2009; Appl. Opt. 2007; J. Biomed. Opt. 2012; Euro. J. Radiol. 2009.

荧光-光学乳腺断层成像

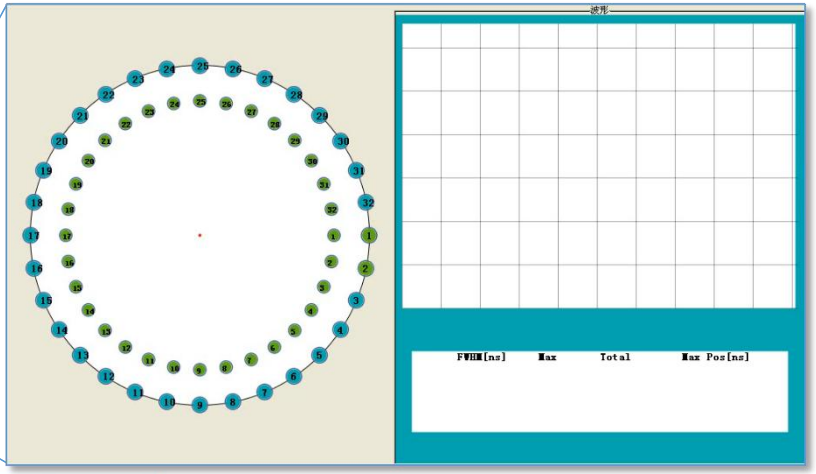
荧光成像的“灯塔”效应

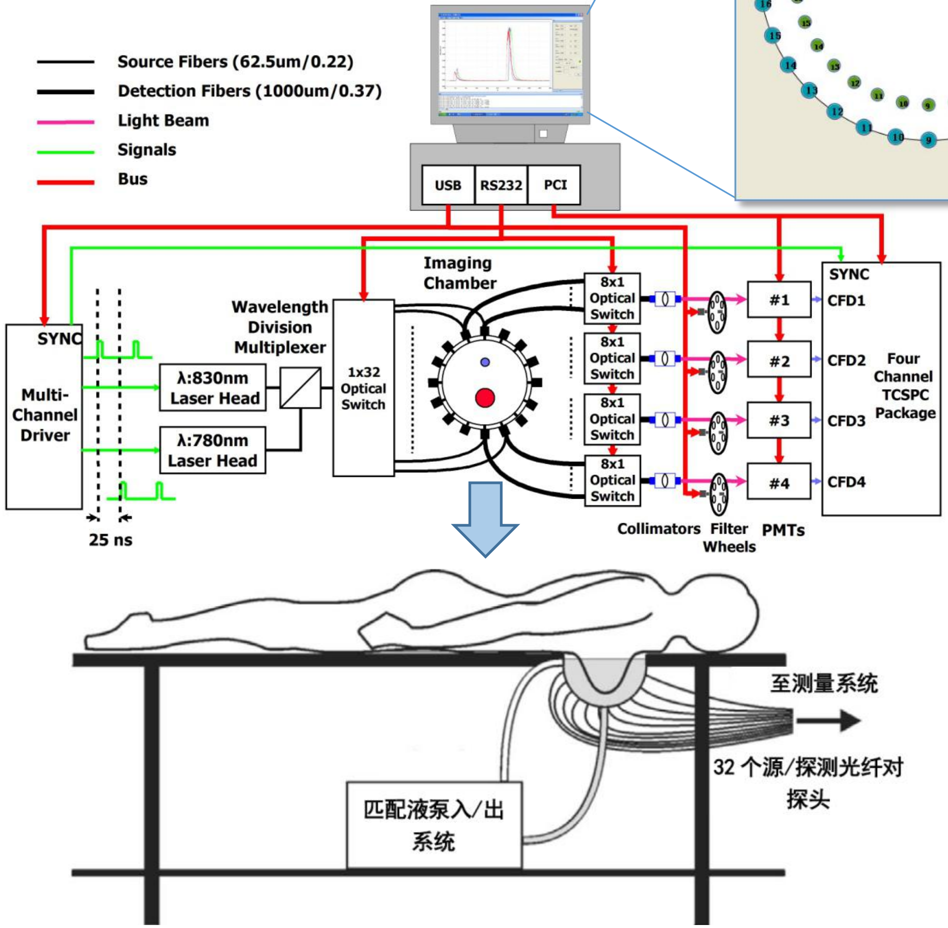


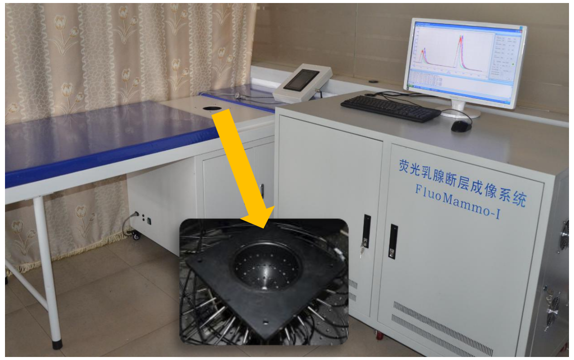


46岁，左乳上可见一肿物影

- 荧光成像的高灵敏性与光学成像的高特异性相结合
- 荧光DOT导航血氧DOT的新方法
- 解决超微弱光检测和多参数图像重建等关键技术难点



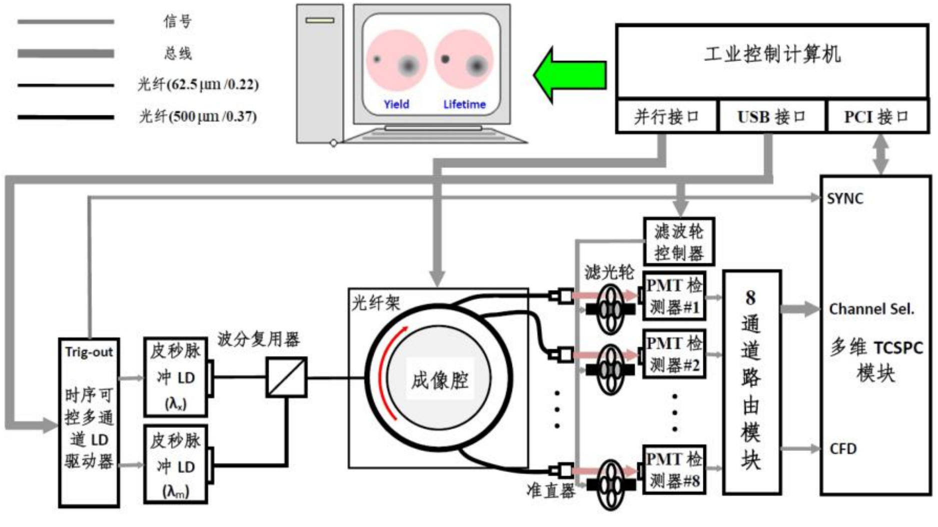




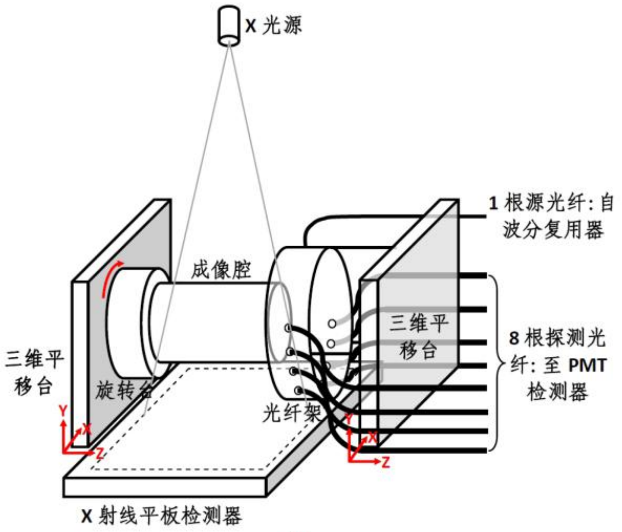
Biomed. Opt. Express 2013; *Appl. Opt.* 2012; *Biomed. Opt. Express* 2015.

DOT/FMT/XCT多模成像

光学结构+时间分辨检测

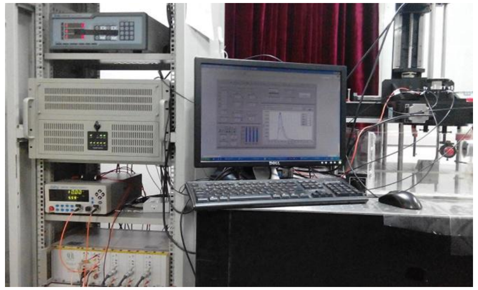


(a)

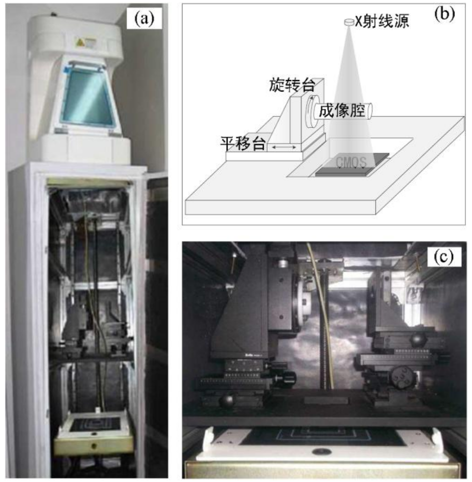


(b)

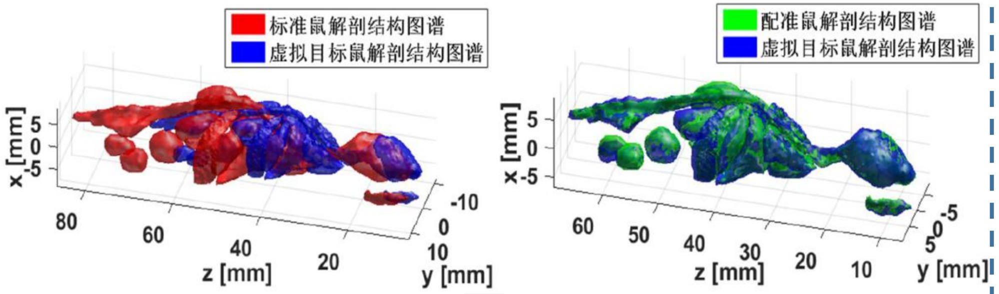
多通道TCSPC系统



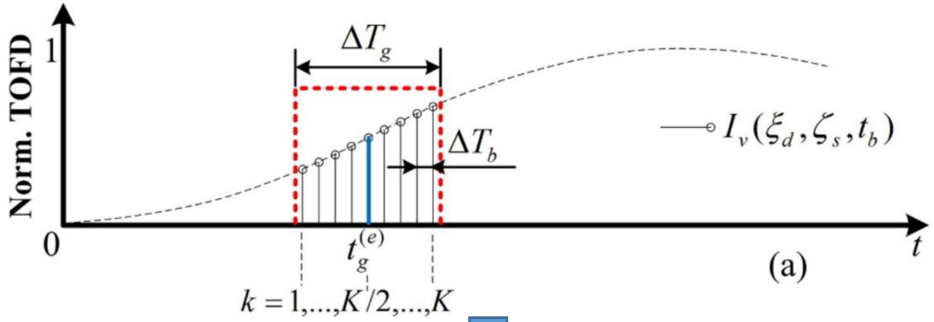
CBCT系统



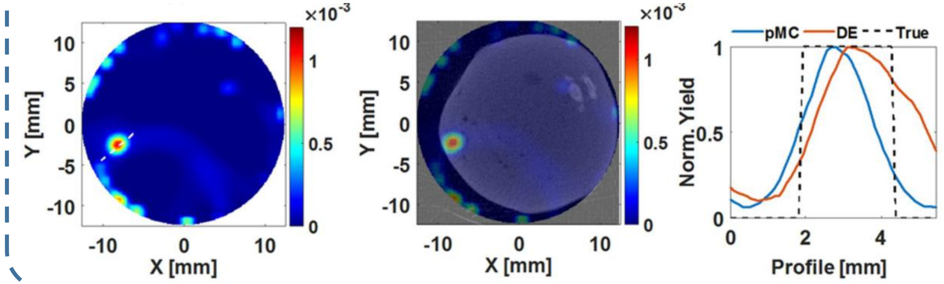
① 基于标准数字鼠配准的光学结构DOT获取



② 全时间分辨-早期光的重叠时间门数据

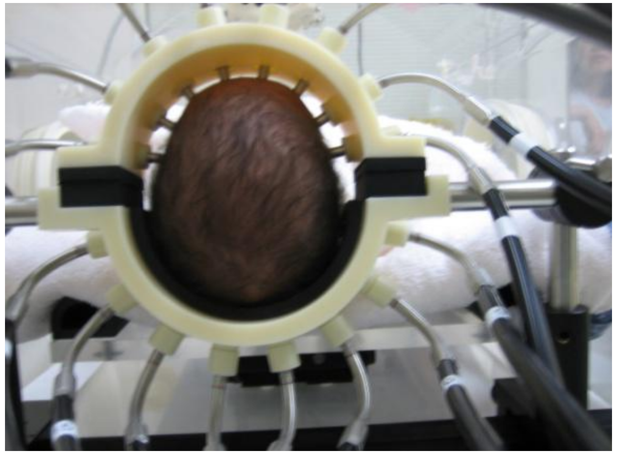


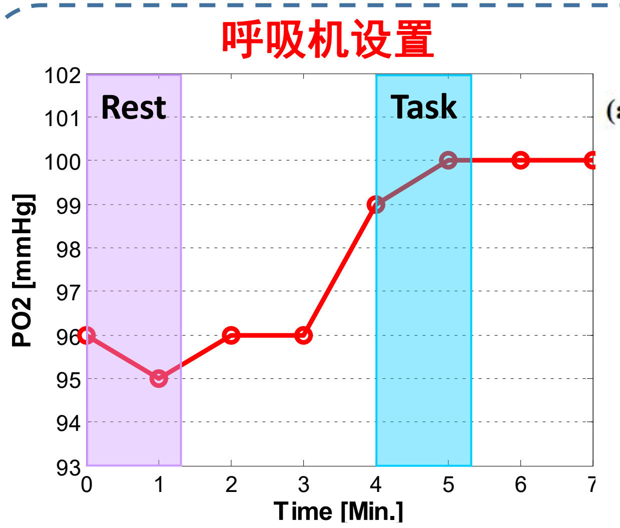
③ 基于pMC时间分辨光子输运模型的FMT

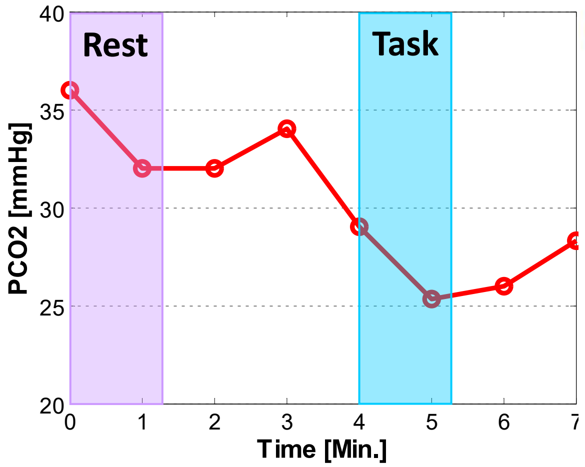


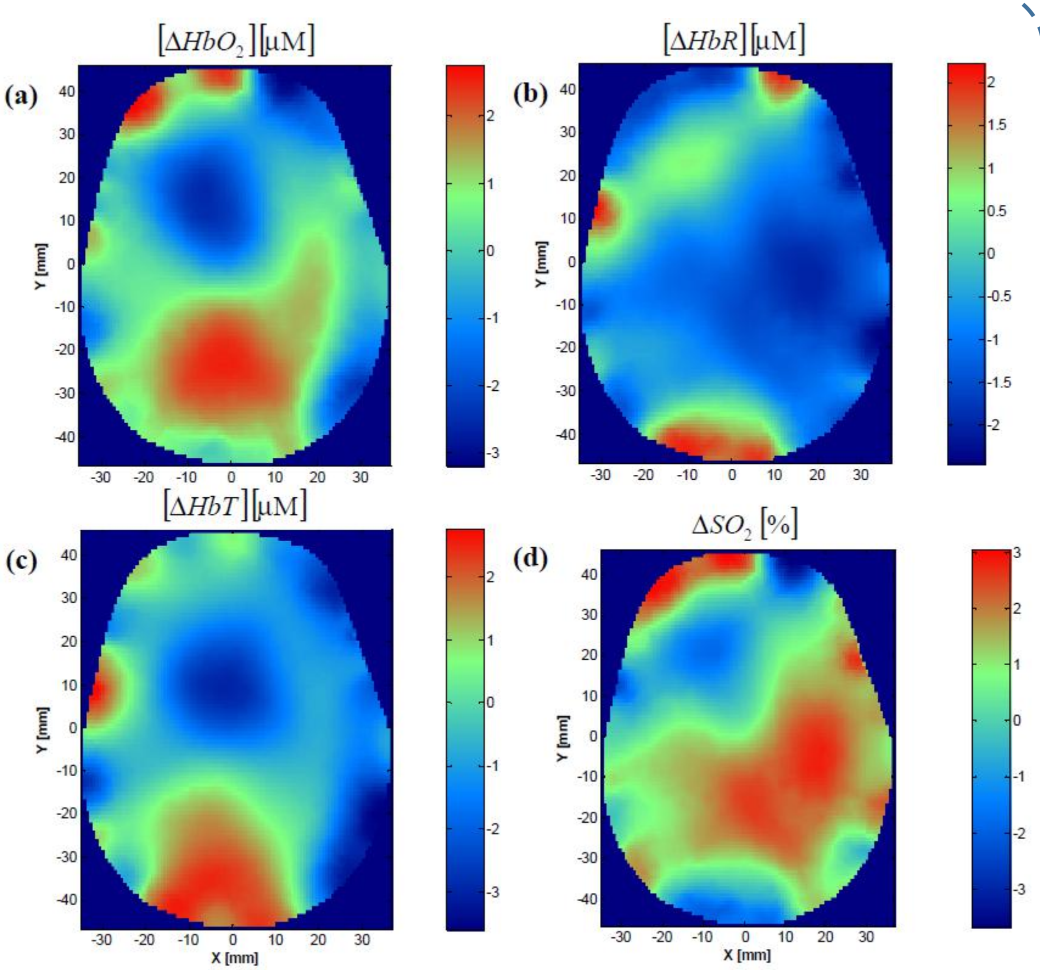
Opt. Express 2008; Appl. Opt. 2002, 2010; Opt. Lett. 2013; Biomed. Opt. Express 2016; Infrared Phys. Tech 2019

新生儿脑发育监护









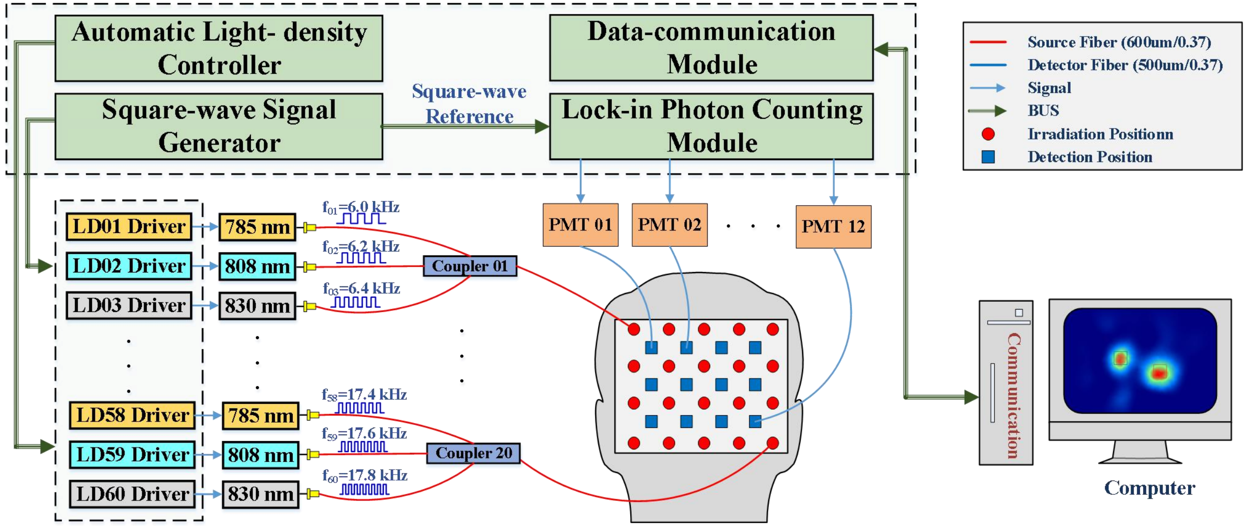
Age: 32-day, Wg: 1065g; Gest. Age: 32 Weeks

J. Biomed. Opt. 2011； *Chin Opt. Lett.* 2006

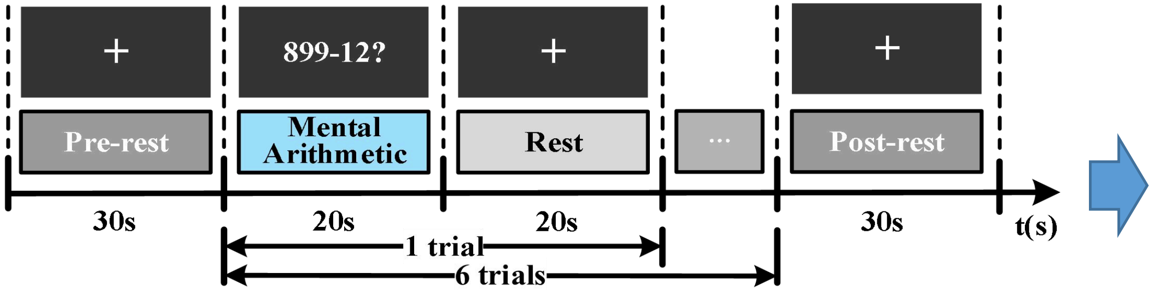
脑功能成像

高灵敏、高密度和大动态测量

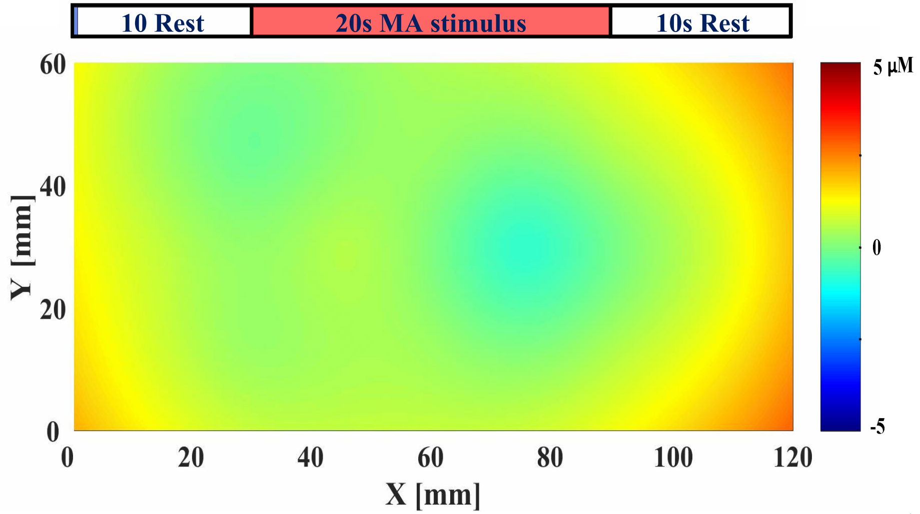
- **锁相光子计数 ->** 全并行源激励下的高灵敏度测量模式
- **交叠区域采集 ->** 严格光子输运模型下定量化和分辨率改善
- **双层拓扑图像 ->** 头皮层干扰和脑皮层功能信号的有效分离



心算范式实验(Mental Arithmetic,MA)



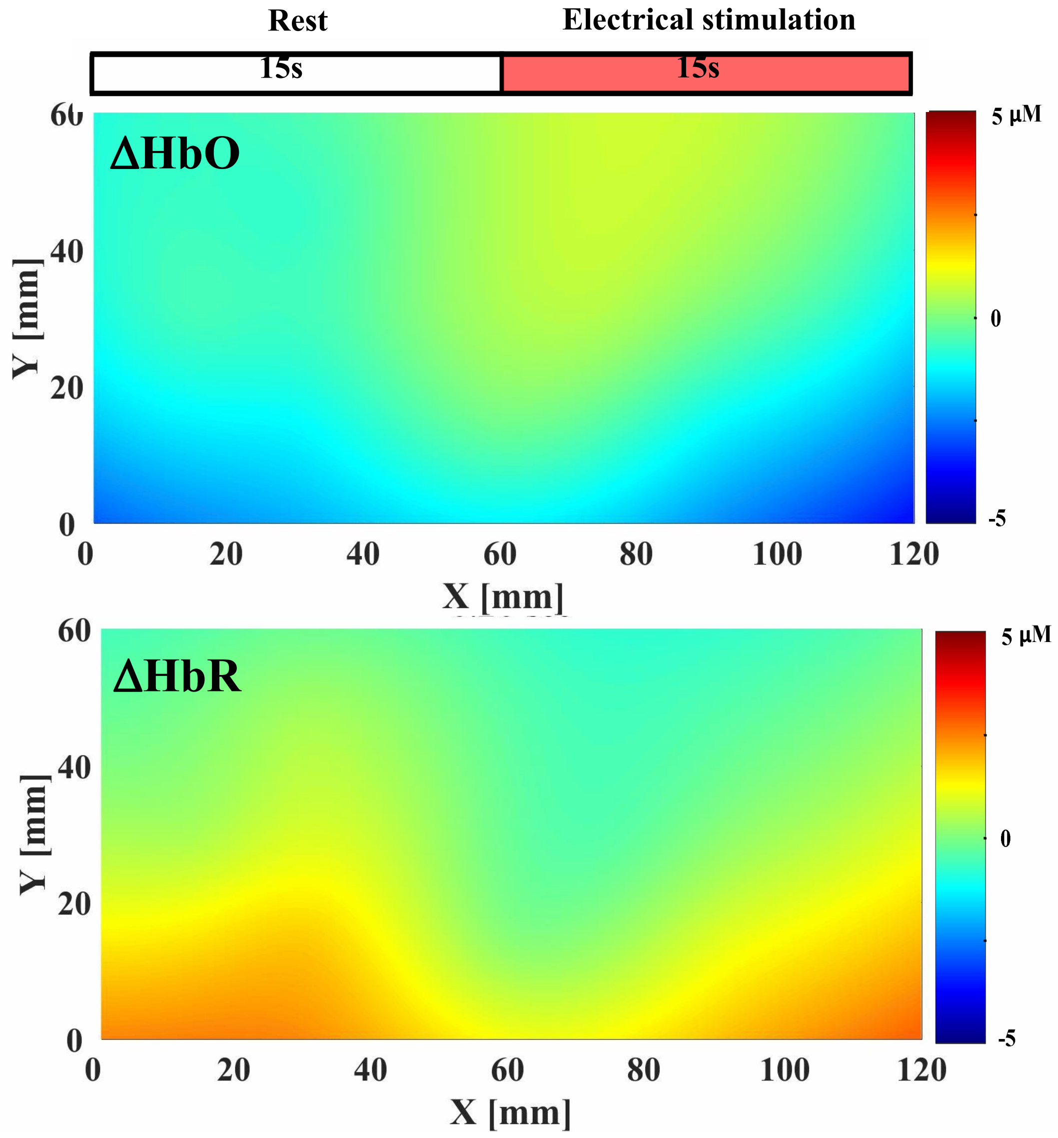
30s的实验前休息和6个单次实验(trial)，每个trial中被试者执行20s心算任务，间隔20s休息，30s实验后休息



Opt. Express 2019; *Appl. Opt.* 2019; *IEEE Access* 2019; *Biomed. Opt. Express* 2020

肌肉组织功能成像

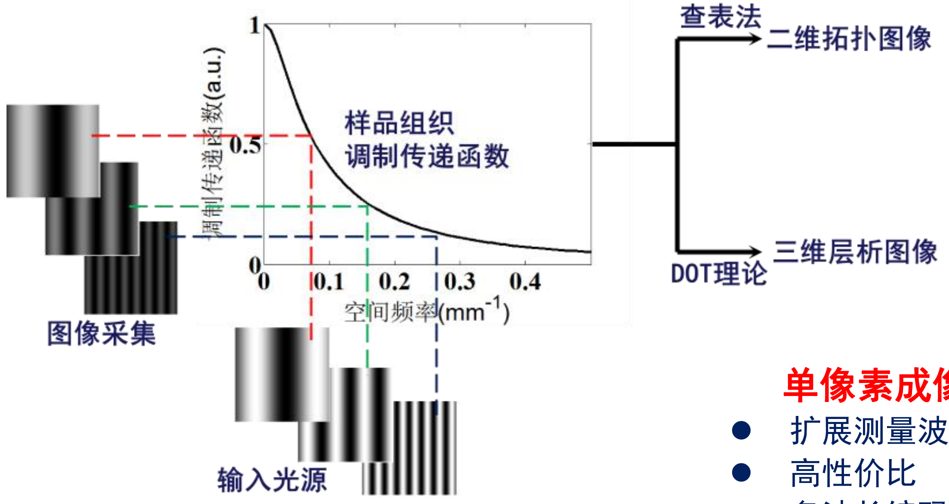
受损脊椎电刺激下fNIRS肌氧监测



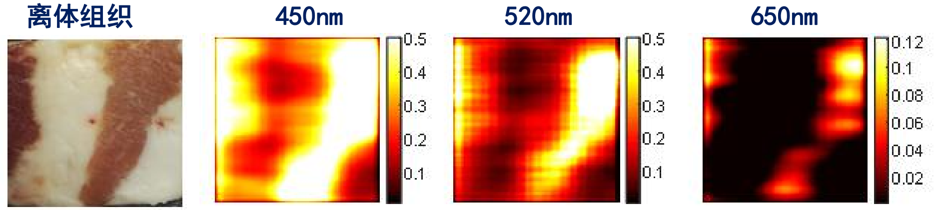
空间频率域成像

快速、宽场、深度分辨成像

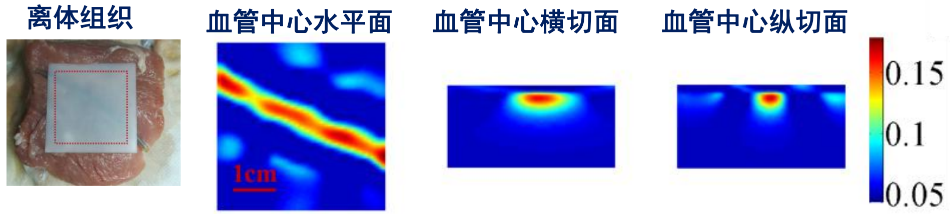
采用正弦调制光照射生物组织并捕捉反射图像，结合光学传输模型来重构出生物组织的光学参数，进而得到与之关联的生理参数作为疾病诊断和测评的依据，非常适合于皮肤、粘膜等浅层组织疾病的诊断及光动力治疗(PDT)过程监测。



离体组织拓扑成像

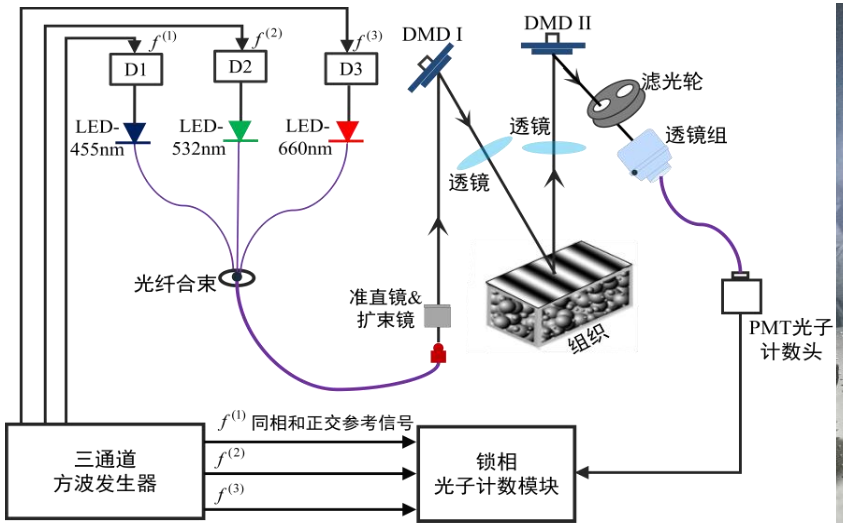


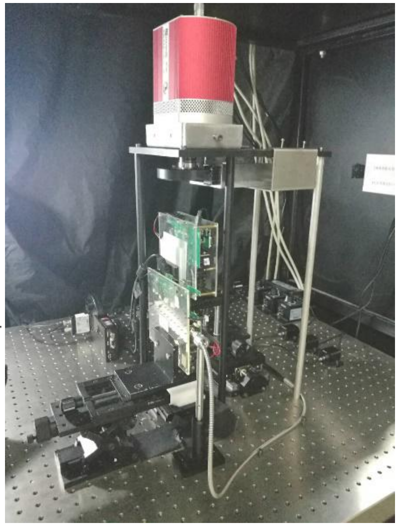
离体组织断层成像

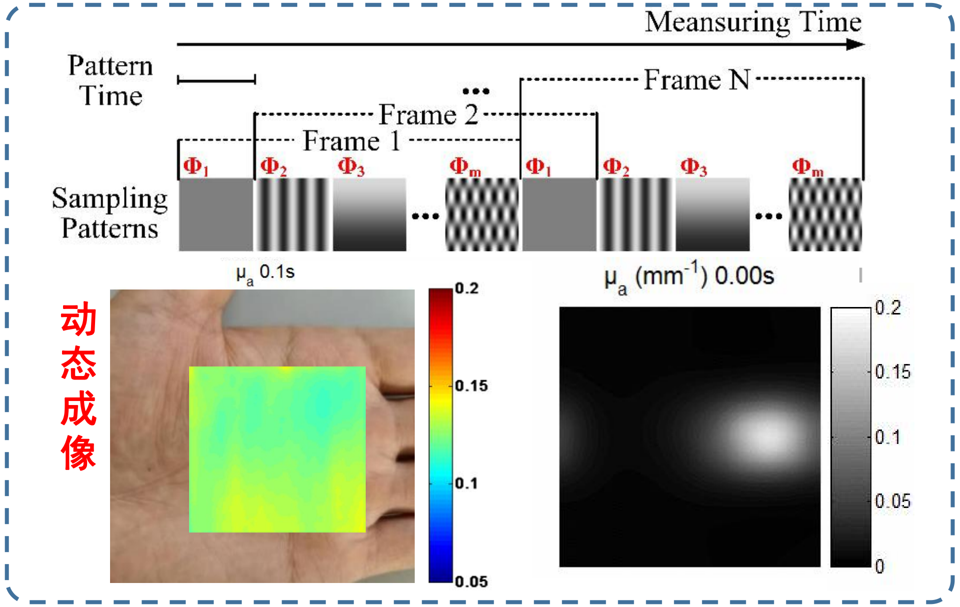


单像素成像

- 扩展测量波段
- 高性价比
- 多波长编码



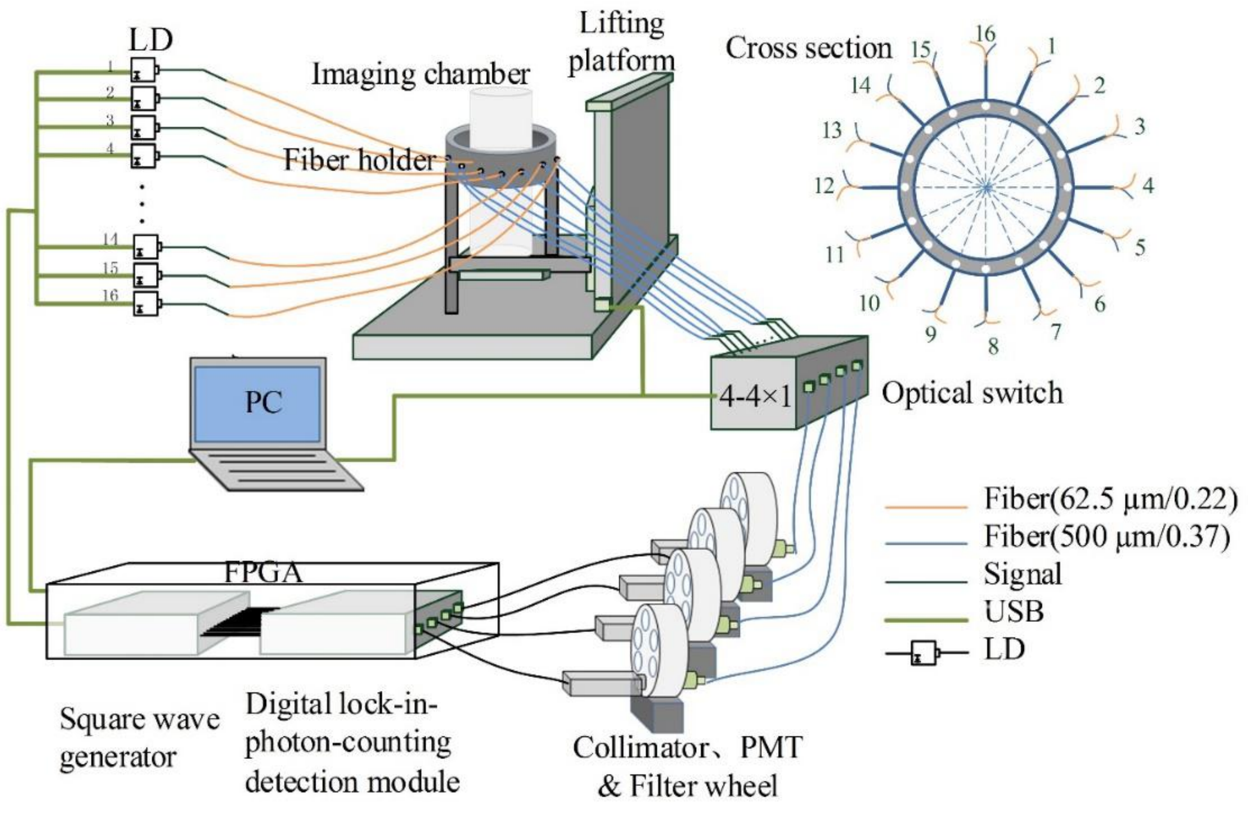


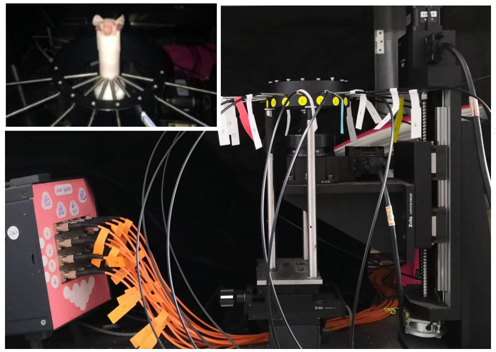


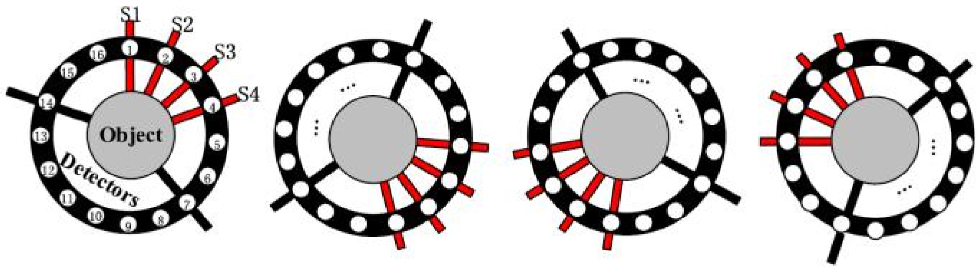
Appl. Opt. 2017; *Opt. Express* 2019

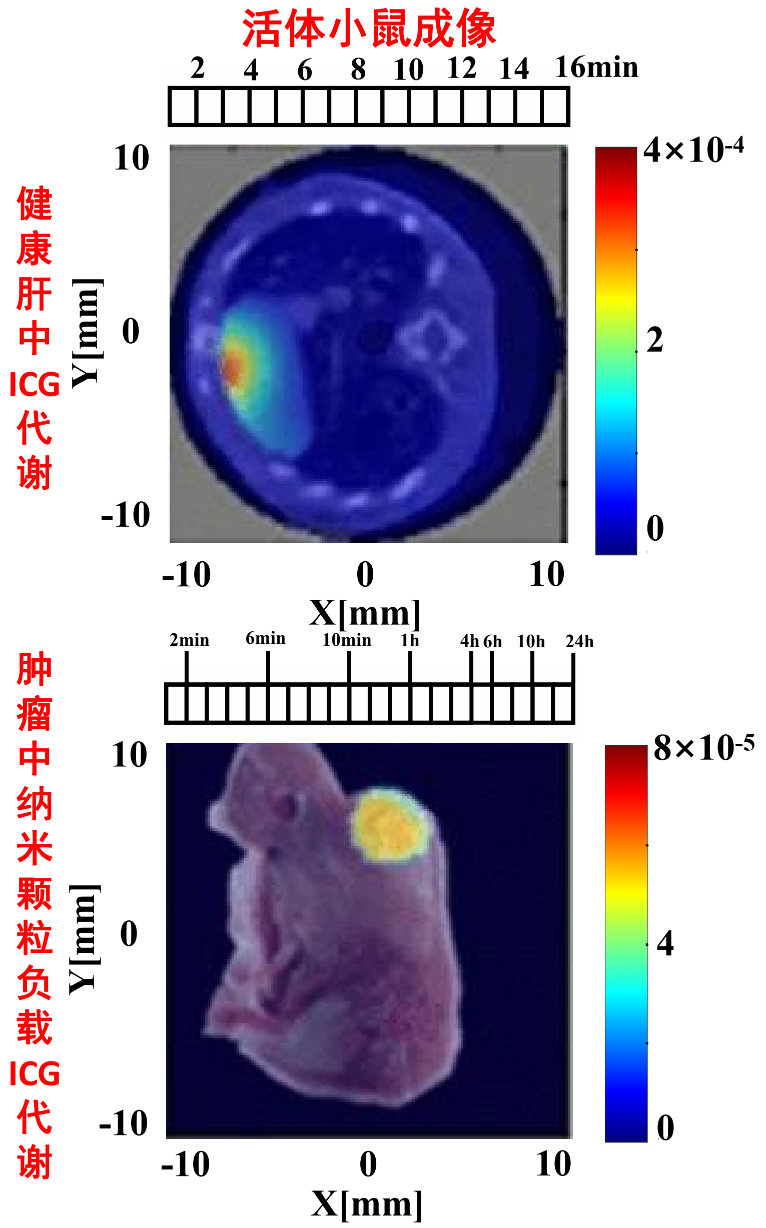
动态荧光层析成像

药代动力学分析



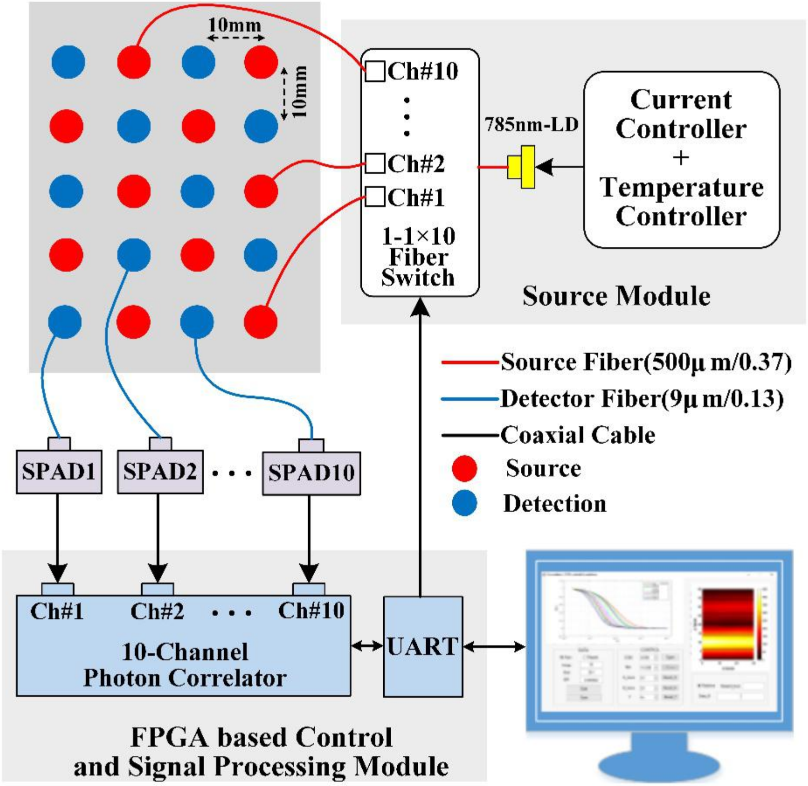


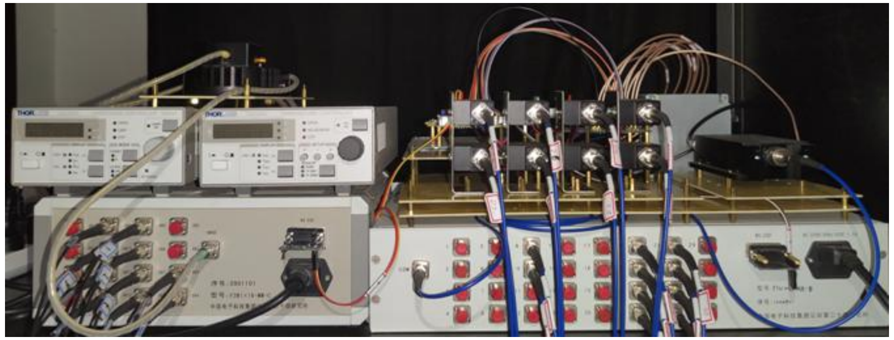




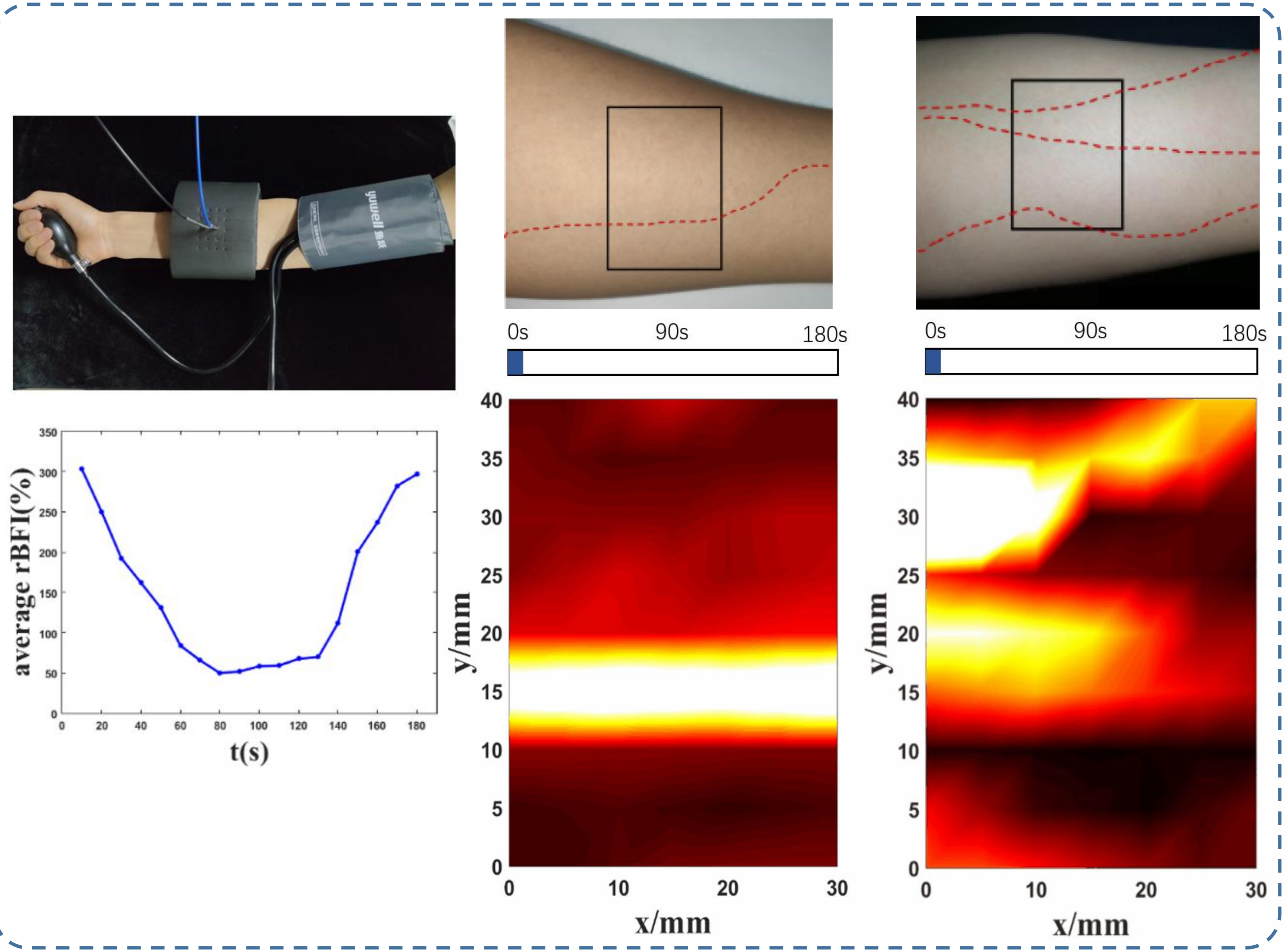
J. Biomed. Opt. 2016; *J. Biophotonics* 2018; *Mol. Imaging Biol.* 2019

扩散光相干光谱(DCS)





静脉阻滞下前臂皮下血管血流成像



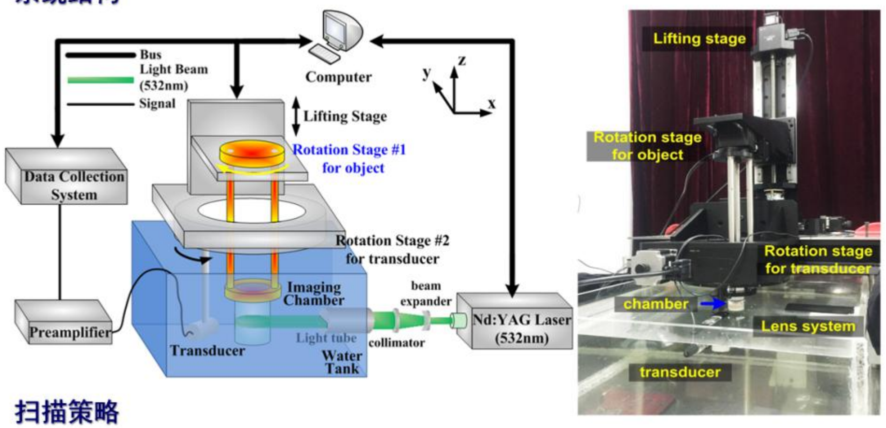
Infrared Phys. Tech. 2020.

定量光声断层成像(q-PAT)

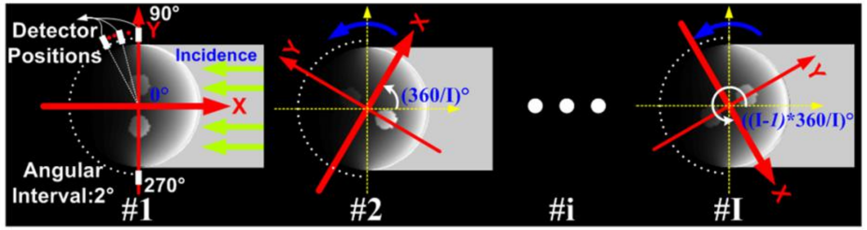
高分辨光学吸收图像

测量系统

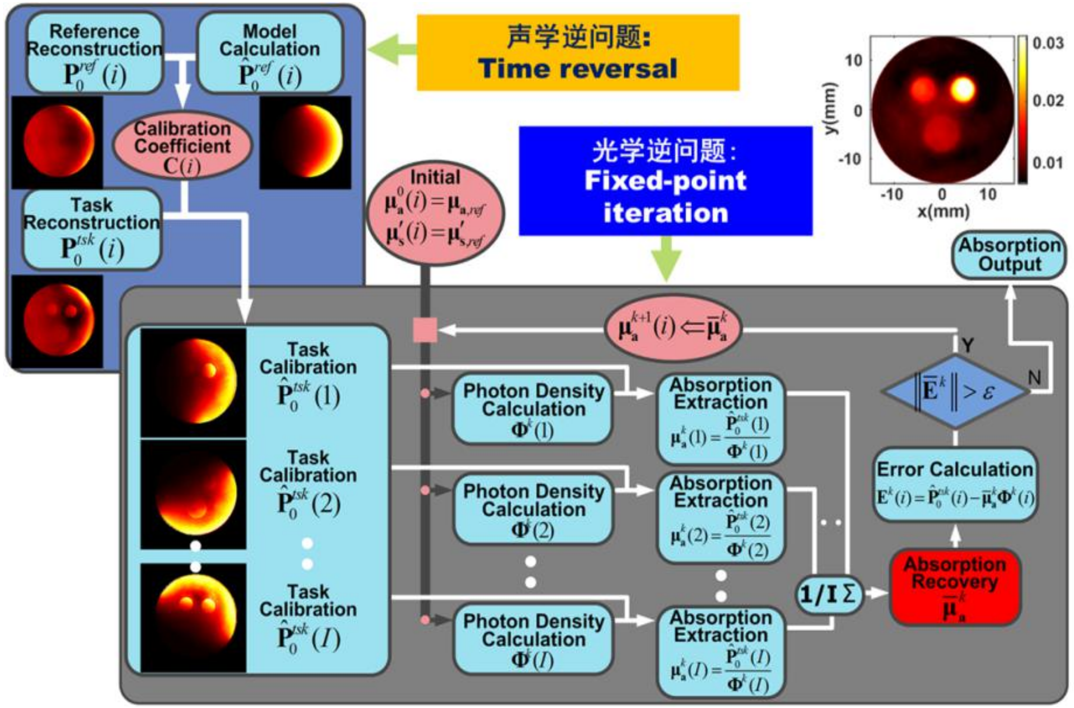
系统结构



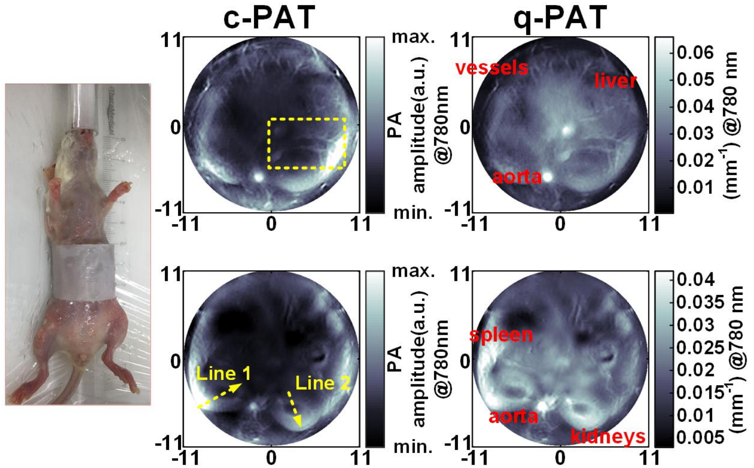
扫描策略



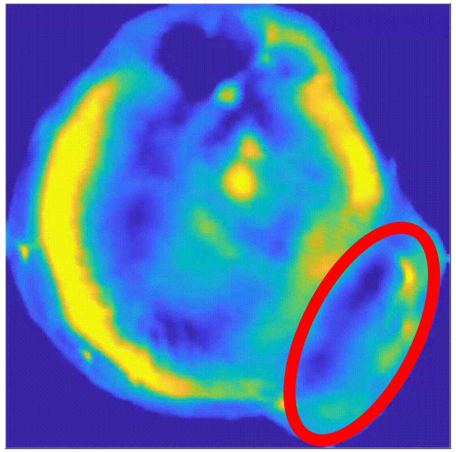
重建策略



活体成像



动态成像



Time post injection of IRDye: 5~35 minutes

tumor region

Appl. Opt. 2016; Biomed. Opt. Express 2017; Biomed. Opt. Express 2018; Photoacoustics 2020; J. Biophotonics 2020.

展望

一、生物组织光子输运模型&图像重建方法

- 在体组织光学结构的获取(结构-功能混合模态成像)
- 光子输运过程的精确模拟(光学复杂域并行Monte-Carlo模拟(
- 深度学习网络方法(Physics-informed or End-to-End)

二、高灵敏、大动态、实时成像技术

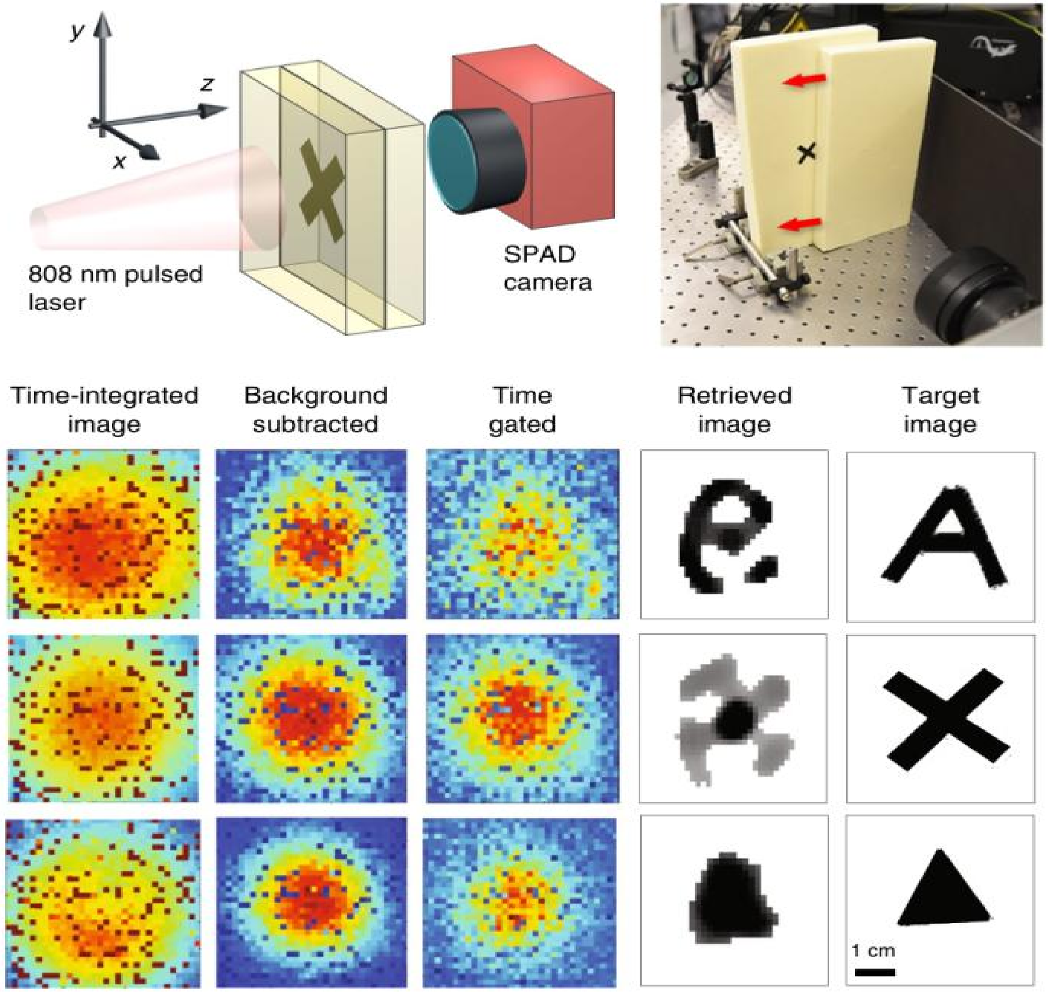
- 新型光电探测技术(SPAD-TDI阵列相机、SiPM探测器、NIR-II探测器)
- 多通道并行“扫描”时域系统 (CDMA技术+同步累加光子计数)
- 宽场(空间频域测量、锁相光子计数)NIR-II/III区成像

三、高定量、多参数实现方案

- 多模态/模式影像融合(MRI、XCT、UI)
- 压缩感知技术和单像素成像
- 血氧动力和药代动力学成像
- NIRS和DCS混合成像 (共系统问题)

四、高效、低毒、高特异性荧光剂

- Omocianine (Philips)
- 纳米量子点



Nature Photon. 2019

致谢

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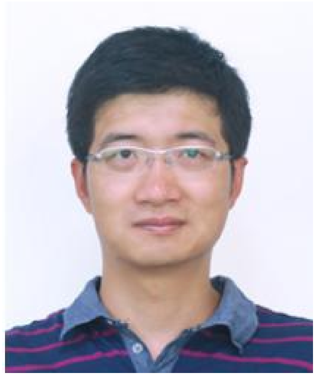
张丽敏副教授



周仲兴副教授

李晨曦讲师

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