Time-Resolved Spectroscopy

with advanced CMOS single photon detector arrays for disease diagnosis in the distal lung

EPSRC Engineering and Physical Sciences Research Council

PROTEUS

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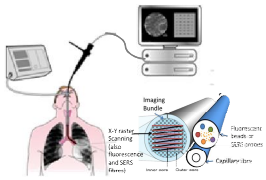
Introduction

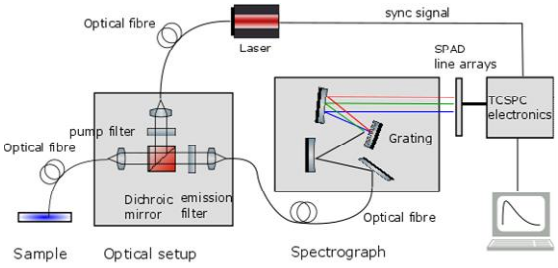
With present diagnostic methods, identification of respiratory illnesses are inexact resulting in an often inaccurate multi-drug treatment. The Proteus project aims for a fibre-based sensing and imaging system to improve disease diagnosis in the distal lung for critically ill patients. For a use with fibre optic sensors a spectrograph for time resolved single photon detection is presented. The system uses a line array of CMOS Single Photon Avalanche Diodes (SPAD) to collect Time-Correlated Single Photon Counting (TCSPC) histograms combining the standard wavelength axis of spectroscopy with the time axis of TCSPC.



Aims

- Recording full TCSPC histograms for 256 pixel simultaneously.
- Distinguish between the tissue autofluorescence and fluorescence from fluorophores in the 'green' spectrum.
- Remove the scattering background from the optical fibre in the 'red spectrum'.
- Sensing of pH variation through changes in the fluorescence lifetime.

The Experimental Setup

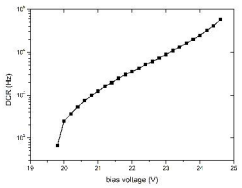


- Point detection of fluorescence using an optical fibre
- Dispersive element to separate the emitted light into its wavelengths
- TCSPC technology for recording dynamical processes

Line Sensor Ra 1

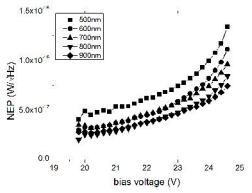
- 256 x 2 pixel,
  1 pixel a column of 4 Single Photon Avalanche Diodes (SPADs)
- Line rate 700 Hz

Dark count rate (DCR)
under experimental conditions

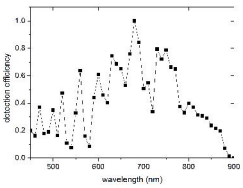


Noise-equivalent-power

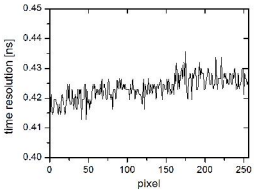
$$NEP = \frac{h\nu}{\eta}\sqrt{2\,DCR} \qquad \nu - photon\ frequency,\ \eta - detection\ efficiency$$



Spectral detection efficiency
Fabry-Perot oscillation between the alternating layers of the CMOS optical stack



Time resolution[1]



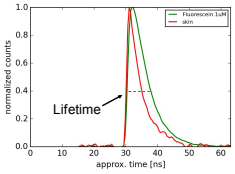
[1]Measurement performed by A Kufcsák

Fluorescence Lifetime Spectroscopy

- measuring intrinsic tissue properties and accurate measurement of fluorescent probes in the distal lung

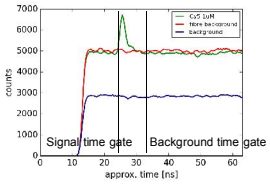
- Fluorescence lifetime is an intrinsic parameter of fluorophores
- Independent of fluorophore concentration, hence fluorescent intensity, and not affected by photobleaching

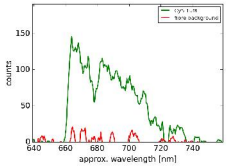
'**Green' spectrum** (500nm – 600nm)
Autofluorescence of tissue and synthesized fluorophores emit in this region.



The autofluorescence of tissue can be resolved and may be used for label free sensing.
The fluorophores with longer fluorescence lifetime can be distinguished from tissue.

'**Red' spectrum** (650nm – 750nm)



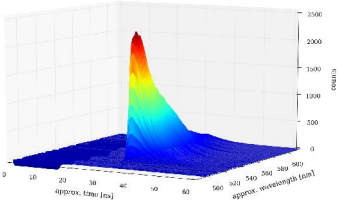


Time gating allows for an easy subtraction of the background from the optical fibre.

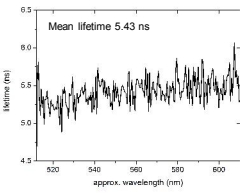
pH Sensing

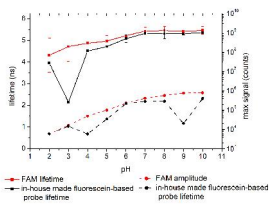
- pH as a potential marker of tissue acid-base status
- a sensing methodology in inflammatory environments, robust to interference from complex biological environments

Fluorescence decay of Fluorescein amidite (FAM) solved in pH 7
Exposure time 5s



Single Exponential Fit with a Least-Square-Method to determine the fluorescence pixelwise





Small changes in the fluorescence lifetime can be measured and used for point sensing of pH in the distal lung.

Reference

[1] J. R. Lankowicz. Principles of Fluorescence Spectroscopy. 3rd edition, Springer, 2010
[2] N. Krstajic et al. "256x2 SPAD line sensor for time resolved fluorescence spectroscopy", Optics Express 23.5, 2015
[3] R. H. Hadfield. "Single-photon detectors for optical quantum information applications", Nature Photonics 3, 2009

Acknowledgements

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