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Time-of-flight laser spectroscopy in biomedical diagnostics

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Optical spectroscopy is becoming a very valuable diagnostic tool in biomedical research. Time-of-flight spectroscopy is a tool providing information regarding scattering and absorption properties of the tissue, valuable for several applications as seen below. In Lund we have in the past developed the technique of supercontinuum generation for spectroscopic investigations of highly scattering media such as tissue[1-3], plant material[4], and pharmaceutical samples[5].

More recently the group in Lund has initiated the development of a unique broadband time-resolved spectroscopy system for turbid media, based on a mode-locked Ti:Sapphire laser pumping a photonic crystal fibre (PCF) and a streak-camera in syncroscan mode.[5,6] The low dispersion of the ultra short laser pulses inside the photonic crystal fibre combined with the small core diameter results in a high peak power of the light in the entire length of the fibre, yielding a high non-linear efficacy resulting in widely spectrally broadened light emission. As a result of this, light pulses with a spectral width spanning from 500 nm to at least 1200 nm were accessible. The streak camera allows recording of time-resolved data with a time resolution of approximately 30 ps. The system is stationary but still relatively flexible and permits both free space as well as fibre coupling of the light onto the sample. This allows different samples and sample geometries to be used. So far direct transmittance (pharmaceutical tablets), fibre coupled transmittance and fibre coupled reflectance (fruits) have been tested. The system has convincingly been used to demonstrate the capability of an analytical instrumentation that could separate absorption and scattering spectra in the evaluation of active substance in pharmaceutical preparations.[7-9] The technique has also been successfully demonstrated for determining the condition of fruits.[10,11]

In contrast to the bulky white light system we have also in parallel been developing a portable diode laser based system for time-resolved measurements.[12] This system is based on the technique called time-correlated single photon counting (TCSPC). This equipment is designed to allow *in vivo* measurement of tissue optical properties of small tissue volumes (less than 1 cm^3) at four wavelengths within the tissue optical window (660, 785, 915 and 970 nm). A lot of effort has gone into making the system portable and suitable for a clinical environment. It is now contained within a box of the approximate size of 50*50*30 cm and the light is coupled via optical fibres to and from the patient/sample. This allows the use of sterile fibres to be unpacked and inserted into the

system inside an operation theatre. The system has been used at clinics for unique local characterisation of breast tissue and the prostate gland.[13,14]
Since both systems, produce similar data (although the diode laser based system is confined to only 4 wavelengths) a general evaluation toolbox based on diffusion theory has been developed within the Lund group. The diffusion models allow the calculation of the scattering and absorption coefficients for each wavelength independently. To get the most from these calculated values several approaches have been developed and tested. For example, in the case of the diode based system, the four different absorption coefficients can be used to calculate the concentration of four tissue constituents (oxy-haemoglobin, deoxy-haemoglobin, fat and water).

The multispectral information provided in fluorescence measurements of lesions located at a certain depth in tissue would, in addition to the diagnostic information that there exist a lesion, also provide depth information useful for reconstruction of fluorescent inclusions in tissue[15,16]. This is one possible concept to improving the robustness and accuracy of the fluorescence tomography reconstructions.

One can now foresee a rapidly increasing interest in time-resolved spectroscopic techniques for medical diagnostics, with the development of molecular markers. Most of the genetically specific markers for optical detection will most probably be based on fluorescence. The computer models for tissue fluorescence are not as developed as for remitted light. An accelerated Monte Carlo simulation routine was developed that is approximately 100 times faster than the conventional model used.[17] This model can be used to partly overcome the lack of other appropriate computer models.

Using very similar ideas we are also developing a new technique to perform on-line dosimetric measurements during interstitial photodynamic therapy[18-20]. This development is conducted in close collaboration with SpectraCure AB, a spin-off company from the group. The company has now integrated a system for interstitial photodynamic therapy of prostate cancer. The system is approved for first clinical studies. Our group has developed the technology concept as well as the dosimetry aspects of the treatments to allow treatment feed-back from the measurements.[21,22]. The main challenge is now to further develop the dosimetry aspects of IPDT and to evaluate the procedure by studying treatment outcome.

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