Analyst

ROYAL SOCIETY OF CHEMISTRY

EDITORIAL

View Article Online
View Journal | View Issue

Cite this: *Analyst*, 2023, **148**, 6143

DOI: 10.1039/d3an90074f

rsc.li/analyst

SPEC 2022: International Conference on Clinical Spectroscopy

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This latest optical diagnosis themed issue of *Analyst*, guest-edited by Dr Aidan D. Meade, Prof. Fiona M. Lyng and Prof. Hugh J. Byrne, all from the Technological University Dublin, is drawn from the participants and proceedings of the International Conference on Clinical Spectroscopy, SPEC 2022, which was held on the 19th–23rd June 2022 in Dublin, Ireland. The conference was chaired by Dr Aidan D. Meade, and co-chaired by Prof. Fiona M. Lyng and Prof. Hugh J. Byrne.

The event was the 12th in the series of biennial conferences, including SPEC 2020, which was due to be held in Monterey, California, but was unfortunately cancelled due to the COVID-19 pandemic. The conference is the flagship of CLIRSPEC, the International Society for Clinical Spectroscopy (https://clirspec.org/), the aim of which is to act as a platform to promote the translation of spectroscopy into the clinical environment, for the general benefit of patients – for example, to improve patient diagnosis and prognosis. In keeping with the translational focus, the aim of SPEC 2022 was to draw together researchers, industrial representatives and clinicians to showcase and advance spectroscopic analysis and imaging towards clinical adoption and to encourage them to influence the direction of future research within the SPEC community.

The conference attracted 225 delegates, from 26 countries, across Europe and beyond, including Australia, Brazil, Canada, Israel, Japan, Sierra Leone, South Korea and the USA, and included contributions from academia, industry, hospitals, and government agencies. The programme was structured around the themes of:

Clinical translational studies;

***In vivo* applications;**

***Ex vivo* applications;**

Therapy monitoring and/or theranostic sensors;

Data science and computational methods;

Advanced/emerging technologies and/or emerging applications/multimodal systems;

and these themes are also reflected in articles collected in this themed issue.

Of particular note in the context of **clinical translational studies** is that of Daoust *et al.* (https://doi.org/10.1039/D2AN01946A) who present their work on the development of a Raman imaging probe system that has been adapted for intraoperative monitoring of tissue margins. The system is mounted on a trolley for ease of bedside deployment, and the probe, mounted on an articulated arm, has a field of view of 1 cm^2, divided into 40 × 42 pixels, each of which provides a spectrum of the tissue over the full fingerprint region of 400–2100 cm^{-1}, with 8 cm^{-1} spectral resolution. The 785 nm source illumination is delivered as a line focus of 10 mm × 400 μm, covering 40 vertical pixels, and is scanned over the 42 lateral pixels, with an exposure time of 7.5 seconds per line. Proof of concept testing of the clinical prototype Raman imaging system, using porcine adipose and muscle tissue, indicated robust classification capabilities, with support vector machine classifiers of specificity, sensitivity and accuracy all exceeding 95%. Significantly, laser and bio-safety, as well as sterilisation considerations, indicated compatibility with the clinical environment. Aaboubout *et al.* further explore the clinical applications of Raman spectroscopy for intraoperative assessment of tumour resection margins to guide oral cancer surgery in the hope of dramatically improving surgical results (https://doi.org/10.1039/D3AN00650F). In contrast to the approach of Daoust *et al.*, a thin single fiber-optic needle probe is inserted into the tissue, from which it measures the Raman spectrum in the high wavenumber region (2600–4000 cm^{-1}). A tissue classification model was developed to discriminate oral cavity squamous cell carcinoma (OCSCC) from healthy oral tissue, with a sensitivity of 0.85 and a specificity of 0.92. Notably, because the Raman spectral response is monitored above 800 nm, the instrument can be operated under ambient room lighting, a critical consideration for intraoperative deployment. Fousková *et al.* also demonstrate the suitability of Raman spectroscopy for ***in vivo* analysis** of tissue, in this instance for the diagnosis of colon cancer (https://doi.org/10.1039/

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D3AN00103B). The analysis was conducted using a custom-built fiber-optic microprobe (11 low-hydroxyl silica collection fibers (d = 200 μm each) surrounding one source fiber (d = 300 μm), enclosed in a nylon casing), coupling the Raman scattering of a 785 nm source to a portable Raman spectrometer. Using several methods of supervised machine learning, over 91% accuracy was achieved in distinguishing colorectal lesions from healthy epithelial tissue, and more than 90% accuracy for classification of premalignant adenomatous polyps. The models enabled the discrimination of cancerous and precancerous lesions with a mean accuracy of almost 92%. Importantly Gautam *et al.* (https://doi.org/10.1039/D3AN00680H) provide an account of the development of phantom technologies for the standardisation of multi-modal spectroscopic systems for *in vivo* applications.

FTIR spectroscopy has also advanced significantly towards clinical translation in recent years, particularly through its use for ***ex vivo* analysis** of human blood serum for diagnosis of brain cancer. The work of Antoniou *et al.* demonstrates that key diagnostic analysis can be performed on the time domain signal, eliminating the need for transformation to the frequency domain spectrum (https://doi.org/10.1039/D2AN02041F). Improved performance of a recurrent neural network model in differentiating between brain cancer and controls was demonstrated in a cohort of 1438 patients, resulting in a mean (cross-validated score) area under the receiver operating characteristic curve of 0.97, and corresponding sensitivity of 0.91 and specificity of 0.91. The study demonstrates that much remains to be explored in the arena of **data science and computational approaches**, and further evidence of the evolution of data science methods for application to chemical imaging histopathology is contained within the work of Ellis *et al.* (https://doi.org/10.1039/D3AN00258F) who introduce a machine learning approach to diagnosis of metastatic oral squamous cell carcinoma (OSCC) based on absorbance ratios. Kujdowicz *et al.* (https://doi.org/10.1039/D2AN01583H) introduce an important Monte Carlo repeated random sampling double cross validation approach to partial least squares discriminant analysis (PLSDA) model tuning for discrimination of bladder cancer, while Ferguson *et al.* (https://doi.org/10.1039/D3AN00618B) introduce a novel approach circumventing the challenge presented by limited availability of training samples for modelling in spectrohistopathology. Their approach trains a repeated partitioning of spectral data within an 'isolation forest' algorithm, whereby leaf depth is used as a metric for differentiation from the main cohort of training spectra. They demonstrate that this approach can detect regions of diseased tissue in testing samples, having been trained only on spectra from normal tissue. Müller *et al.* (https://doi.org/10.1039/D3AN00166K) provide a detailed study on the effect of dimensionality reduction of spectral images on learning of neural networks, observing that network performance is relatively invariant with the dimensionality reduction approach, suggesting they typically learn on spatial rather than spectral features. Al Jedani *et al.* (https://doi.org/10.1039/D3AN00692A) also demonstrate the application of a regression approach to fusion of spectroscopic and H&E images, an important area for advancement towards spectrohistopathology ***ex vivo***.

A number of further contributions describe ***ex vivo* applications** of vibrational spectroscopy using biofluid and cellular samples. Bonizzi *et al.* (https://doi.org/10.1039/D3AN00051F) demonstrate the ability of Raman spectroscopy to provide a measure of the quality of lipoproteins (LPs) in blood samples. Raman spectra recorded from LPs extracted from plasma showed an altered biochemical profile and oxidation state of LPs from obese patients (n = 39) compared to those from healthy controls (n = 26). Dragounová *et al.* (https://doi.org/10.1039/D3AN00679D) describe a study on the identification of bacteria in urine samples with mixed infections. Two classification models were developed using Raman spectral data from clinical isolates to identify the Gram type (two-class model) and bacterial family (six-class model). These models were then applied to artificial mixtures from the clinical isolates and to urine samples from patients with suspected urinary tract infections (n = 59). In the artificial mixtures, Gram type could be identified with 75% accuracy but bacterial family could not be predicted accurately. Translation to the patient urine samples proved difficult, which may be due to differences in the spectra of bacteria after isolation and cultivation. Bui *et al.* (https://doi.org/10.1039/D3AN00806A) show that Raman spectra of extracellular vesicles (EVs) extracted from bile samples from healthy controls (n = 4), and patients with hepatocellular cancer (n = 8) and gall bladder polyps (n = 21) can be discriminated from patients with gall bladder cancer (n = 5).

Guliev *et al.* (https://doi.org/10.1039/D3AN00074E) demonstrate the potential of high throughput Raman spectroscopy for ***ex vivo*** characterisation of intra-epithelial lymphocytes from a mouse model of small intestinal inflammation. Cells isolated from mice that received T-cell transfer could be discriminated from those of untreated mice on the basis of prominent nucleic acid spectral features. Using primary tongue cells from patients with oral squamous cell carcinoma (n = 3), Notarstefano *et al.* (https://doi.org/10.1039/D3AN01182H) show the ability of Raman spectroscopy to monitor the cell death response to cisplatin **therapy** over the course of 72 hours. Multivariate curve resolution–alternating least squares (MCR–ALS) was used to elucidate response rates and in the future, the method could potentially be developed as a companion diagnostic to test individual patient responses to drugs. Finally, Monaghan *et al.* (https://doi.org/10.1039/D3AN00686G) demonstrate the exquisite sensitivity of spectroscopic methods to sample preparation protocols and supply some recommendations in this regard for blood biopsies.

Advanced methods for *ex vivo* surgical support using, respectively, spatially offset and high-wavenumber Raman spectroscopies are presented by Vardaki *et al.* (https://doi.org/10.1039/D3AN00684K) and Haskell *et al.* (https://

doi.org/10.1039/D3AN00574G). Each demonstrate the potential for approaches such as these to support in-surgery precision diagnosis and treatment. Tang *et al.* (https://doi.org/10.1039/D3AN00119A) provide an account of the development and proof-of-concept of a purpose-built Raman microscope for the ultimate objective of the classification of bladder cancer cells within urine, while Vrtělka *et al.* (https://doi.org/10.1039/D3AN00164D) demonstrate that a **multi-modal** approach involving ATR-FTIR, electronic circular dichroism, Raman spectroscopy and Raman optical activity can provide improved diagnostic performance in discriminating liver cancer from liver cirrhosis. Gautam *et al.* (https://doi.org/10.1039/D3AN00680H) provide an account of the development of phantom systems simulating optical transport for *ex vivo* validation of diagnostic optical spectroscopic systems.

Studies on the development of **spectroscopic sensors** for biofilms and biofluids are provided by Tatar *et al.* (https://doi.org/10.1039/D3AN00682D) and Aljuhani *et al.* (https://doi.org/10.1039/D3AN00301A).

This special issue provides an overview of the contributions by researchers in the clinical spectroscopy community to the SPEC 2022 meeting in Dublin. Indeed, the progress of the field can be gauged in the context of the themed issues of the previous meetings in 2008 (https://doi.org/10.1039/B907715B), 2010 (https://doi.org/10.1039/C005546H), 2012 (https://doi.org/10.1039/C3AN90052E), 2014 (https://doi.org/10.1039/C5AN90024G), 2016 (https://doi.org/10.1039/C7AN90013A), and 2018 (https://doi.org/10.1039/C8AN90098A). Undoubtedly, significant progress has been made towards translation to the clinical environment, and in respect of the sophistication of the associated analytical techniques and the data analysis protocols. We thank all the contributors and look forward to SPEC 2024 in Ioannina, Greece (https://spec2024.com/).